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PROGRAMA DE PÓS-GRADUAÇÃO EM NEUROLOGIA
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**ALTERAÇÕES COGNITIVAS APÓS CIRURGIAS DE PEQUENO PORTE:
ATENÇÃO SUSTENTADA COMO MARCADOR DE RECUPERAÇÃO COGNITIVA
E PRONTIDÃO PARA ALTA HOSPITALAR**

RIO DE JANEIRO
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Tese apresentada ao Programa de Pós-Graduação em Neurologia do Centro de Ciências Biológicas e da Saúde da Universidade Federal do Estado do Rio de Janeiro, como requisito parcial para a obtenção do título de Doutor em Neurologia, área de concentração Neurociências.

Orientador: Prof. Dr. Sergio Luis Schmidt

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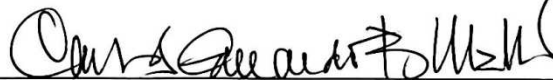
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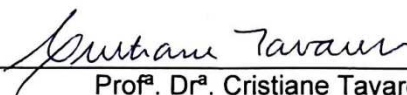
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Dedico esta tese à minha família, fonte permanente de amor, apoio e inspiração.

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"It always seems impossible until it's done."

Nelson Mandela

(1918-2013)

RESUMO

Introdução: A existência de alterações cognitivas transitórias no pós-operatório imediato, mesmo após cirurgias de pequeno porte, permanece uma questão relevante na medicina perioperatória. Embora frequentemente sutis, essas alterações podem comprometer a compreensão das orientações de alta, a tomada de decisões e o retorno seguro às atividades habituais, potencialmente afetando a segurança e a autonomia do paciente no momento da alta hospitalar. **Objetivo:** O objetivo principal é investigar a ocorrência de alterações cognitivas após cirurgias de pequeno porte no momento da alta, sob anestesia geral, através de uma bateria de testes neuropsicológicos e os objetivos secundários são avaliar possível influência da técnica anestésica nos desfechos cognitivos e investigar alterações cognitivas pós-operatórias nos dias 15 e 45 de pós-operatório. **Métodos:** Foi conduzido um estudo clínico comparando pacientes submetidos a cirurgia com indivíduos não operados, e secundariamente, comparou-se pacientes submetidos a anestesia venosa total baseada em propofol ou à anestesia inalatória baseada em sevoflurano durante colecistectomia videolaparoscópica eletiva. A avaliação neuropsicológica incluiu o Computerized Visual Attention Test (CVAT), o Controlled Oral Word Association Test (COWAT), o Symbol Digit Modalities Test (SDMT) aplicados no pré-operatório, na alta hospitalar, aos 15 e aos 45 dias após a cirurgia. Para análise dos resultados, foi calculado um delta de mudança relativa, definido como diferença proporcional entre desempenho pré-operatório e o desempenho pós-operatório ((pré-operatório - pós-operatório) / pré-operatório). As diferenças entre os grupos foram analisadas por meio de análise multivariada de variância (MANOVA) bicaudal, seguida de análises univariadas de variância (ANOVA) e comparações múltiplas pós-hoc com ajuste de Bonferroni, quando apropriadas. Esta tese deriva de um protocolo mais amplo, prospectivo registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC RBR-6xhp399; UTN U1111-1295-3640) e aprovado pelo Comitê de Ética em Pesquisa da UNIRIO. **Resultados:** Um total de 105 participantes foi incluído na análise (37 não cirúrgicos, 34 no grupo propofol e 34 no grupo sevoflurano). A MANOVA demonstrou um efeito significativo de grupo (traço de Pillai = 0,332; $p < 0,001$; $\eta^2 = 0,196$). As análises univariadas (ANOVAs) revelaram diferenças significativas nos domínios de atenção sustentada (CVAT), fluência verbal (COWAT) e função executiva/velocidade de processamento (SDMT) na alta hospitalar. O grupo propofol apresentou declínio mais acentuado da atenção sustentada em comparação ao grupo não cirúrgico. Na fluência verbal, o grupo não cirúrgico apresentou melhora na avaliação do dia seguinte, enquanto ambos os grupos cirúrgicos não demonstraram melhora, indicando desempenho relativamente pior. No SDMT, o grupo sevoflurano apresentou desempenho inferior em relação aos demais grupos. Não foram observadas diferenças persistentes entre os grupos nas avaliações de 15 e 45 dias. **Conclusão:** Pacientes submetidos a cirurgias de pequeno porte podem apresentar alterações cognitivas transitórias no momento da alta hospitalar, independente da técnica anestésica empregada. A atenção sustentada se apresentou como domínio cognitivo mais vulnerável, e se mostrou potencial como biomarcador da recuperação cognitiva pós-operatória. Este resultado sugere padronização de avaliação neuropsicológica sistemática nos pacientes submetido a cirurgias de pequeno porte.

Palavras-chave: Anestesia. Atenção. Alterações cognitivas pós-operatórias. Propofol. Sevoflurano. Anestesia intravenosa. Anestesia inalatória.

ABSTRACT

Background: The occurrence of transient cognitive changes during the immediate postoperative period, even after minor surgical procedures, remains an important concern in perioperative medicine. Although often subtle, these changes may impair patients' ability to understand discharge instructions, make decisions, and safely resume their usual activities, potentially compromising patient safety and autonomy at the time of hospital discharge. **Objective:** To investigate the occurrence of cognitive changes following minor surgery under general anesthesia at the time of hospital discharge using a battery of neuropsychological tests. Secondary objectives were to evaluate the influence of anesthetic technique on cognitive outcomes and to investigate cognitive performance 15 and 45 days after surgery. **Methods:** A clinical study was conducted comparing surgical patients with non-surgical controls and, secondarily, comparing patients receiving propofol-based total intravenous anesthesia or sevoflurane-based inhalational anesthesia during elective laparoscopic cholecystectomy. Neuropsychological assessment included the Computerized Visual Attention Test (CVAT), the Controlled Oral Word Association Test (COWAT), and the Symbol Digit Modalities Test (SDMT), administered preoperatively, at hospital discharge, and 15 and 45 days after surgery. Relative change scores (delta values) were calculated as the proportional difference between preoperative and postoperative performance ((preoperative – postoperative performance)/preoperative performance). Group differences were analyzed using two-tailed multivariate analysis of variance (MANOVA), followed by univariate analyses of variance (ANOVA) and Bonferroni-adjusted post hoc comparisons when appropriate. This thesis derives from a broader prospective protocol registered in the Brazilian Registry of Clinical Trials (ReBEC RBR-6xhp399; UTN U1111-1295-3640) and approved by the Research Ethics Committee of the Federal University of the State of Rio de Janeiro.

Results: A total of 105 participants were included in the analysis (37 non-surgical controls, 34 in the propofol group, and 34 in the sevoflurane group). MANOVA demonstrated a significant group effect (Pillai's trace = 0.332, $p < 0.001$, $\eta^2 = 0.196$). Univariate analyses revealed significant differences in sustained attention (CVAT), verbal fluency (COWAT), and processing speed/executive function (SDMT) at hospital discharge. The propofol group exhibited a greater decline in sustained attention compared with the non-surgical group. In verbal fluency, the non-surgical group showed improvement consistent with a practice effect, whereas both surgical groups failed to demonstrate similar gains. In the SDMT, the sevoflurane group showed poorer performance than the other groups. No persistent between-group differences were observed at the 15- and 45-day follow-up assessments.

Conclusions: Patients undergoing minor surgery may experience transient cognitive changes at the time of hospital discharge, regardless of the anesthetic technique employed. Sustained attention emerged as the most vulnerable cognitive domain and showed potential as a biomarker of postoperative cognitive recovery. These findings reinforce that clinical discharge does not necessarily indicate complete cognitive recovery and support the incorporation of objective cognitive assessments into modern perioperative care.

Keywords: Anesthesia. Attention. Postoperative cognitive dysfunction. Propofol. Sevoflurane. Anesthesia intravenous. Anesthesia inhalation.

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LISTA DE ABREVIATURAS E SIGLAS

CAAE	<i>Ethics committee ID code (not expanded in the text)</i>
CAM-ICU	<i>Confusion Assessment Method for the Intensive Care Unit</i>
CE	Erros de Comissão
COWAT	<i>Controlled Oral Word Association Test</i>
CVAT	<i>Computerized Visual Attention Test</i>
FAS	Fonemas F, A e S
OE	Erros de Omissão
RBR-6xhp399	Código do registro do ensaio clínico (ReBEC)
ReBEC	Registro Brasileiro de Ensaios Clínicos
RT	Tempo de Reação
SDMT	<i>Symbol Digit Modalities Test</i>
U1111-1295-3640	UTN código de identificação do estudo (número)
UTN	Código de identificação do estudo
VRT	Variabilidade do Tempo de Reação

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1 CONTEXTUALIZAÇÃO E ESTRUTURA DA TESE

Meu envolvimento com a linha de pesquisa que originou esta tese teve início em 2020, durante os primeiros meses da pandemia de COVID-19. Naquele momento, fui convidada pelo Prof. Dr. Sérgio Luís Schmidt para integrar sua equipe de pesquisa no Hospital Universitário Gaffrée e Guinle (HUGG/UNIRIO), participando do projeto intitulado “*Manifestações Neuropsicológicas Durante a Pandemia COVID-19*, incluindo comparações de respostas via internet e por entrevista direta”, aprovado pelo Comitê de Ética em Pesquisa do HUGG sob o parecer nº 5.187.287 (CAAE: 54581221.0.0000.5258) (Anexo A).

A partir de maio de 2020, passei a atuar diretamente na coleta de dados do estudo, que avaliou profissionais de saúde do hospital envolvidos na assistência durante a pandemia. Além da aplicação de questionários padronizados relacionados a aspectos emocionais, comportamentais e ocupacionais, os participantes eram submetidos à avaliação objetiva da atenção por meio do Teste Computadorizado de Atenção (TCA), instrumento desenvolvido para mensurar diferentes subdomínios atencionais.

Essa experiência representou meu primeiro contato com pesquisas neuropsicológicas de campo e permitiu minha familiarização com a aplicação de testes cognitivos computadorizados, com os procedimentos de coleta sistemática de dados e com os fundamentos teóricos relacionados à avaliação da atenção. Durante o desenvolvimento do projeto, tive a oportunidade de acompanhar todas as etapas da pesquisa, desde o recrutamento dos participantes até a análise e interpretação dos resultados, ampliando significativamente meu interesse pelos mecanismos cognitivos envolvidos em diferentes condições clínicas (Apêndices A a D).

Os resultados desse estudo demonstraram que profissionais de saúde expostos às condições extremas de trabalho durante a pandemia apresentavam alterações mensuráveis em diferentes componentes da atenção, reforçando a sensibilidade desse domínio cognitivo a situações de estresse fisiológico e emocional. A participação nesse projeto despertou meu interesse pela investigação da atenção sustentada como possível marcador de vulnerabilidade cognitiva e abriu caminho para minha inserção definitiva na linha de pesquisa coordenada pelo Prof. Sérgio Schmidt.

Nos anos subsequentes, tive a oportunidade de participar de outras investigações conduzidas pelo grupo, envolvendo diferentes populações clínicas e a utilização de instrumentos neuropsicológicos computadorizados para avaliação da atenção. Esse contato progressivo com a pesquisa em neuropsicologia permitiu compreender a importância da atenção sustentada como um dos componentes mais sensíveis do funcionamento cognitivo humano e seu potencial aplicação como biomarcador em diferentes contextos clínicos.

Paralelamente à minha atuação como anestesiológista, passou a despertar especial interesse a possibilidade de aplicar esses conhecimentos ao contexto perioperatório. A observação cotidiana de pacientes submetidos a procedimentos cirúrgicos, frequentemente considerados aptos para alta hospitalar com base exclusivamente em critérios clínicos e fisiológicos, suscitou o questionamento sobre a existência de alterações cognitivas transitórias não identificadas pelas avaliações convencionais.

A partir dessa reflexão surgiu a proposta de investigar sistematicamente as alterações cognitivas após cirurgias de pequeno porte, inicialmente com foco na comparação entre diferentes técnicas anestésicas. Contudo, à medida que os resultados foram sendo produzidos, tornou-se evidente que a principal contribuição científica da investigação não estava relacionada à comparação entre agentes anestésicos, mas sim à identificação da atenção sustentada como um potencial marcador da recuperação cognitiva pós-operatória (Apêndice E).

Dessa forma, a presente tese representa a continuidade natural de uma trajetória científica iniciada durante a pandemia de COVID-19, consolidada por meio da participação em diferentes projetos de pesquisa em neuropsicologia e culminando na investigação da atenção sustentada como biomarcador da recuperação cognitiva após cirurgia e anestesia.

Esta tese se insere na linha de pesquisa de “Neurologia do Comportamento” do Programa de Pós-Graduação em Neurologia da UNIRIO (PPGNEURO).

2 FUNDAMENTAÇÃO TEÓRICA E REVISÃO DA LITERATURA

O número de cirurgias de ambulatoriais realizadas anualmente está crescendo em todo o mundo e a qualidade da recuperação perioperatória não pode ser negligenciada pelo sistema de saúde (NIHR Global Health Unit on Global Surgery; CovidSurg Collaborative, 2022). Com a expansão dos programas de cirurgia ambulatorial e dos protocolos de recuperação acelerada, um número cada vez maior de pacientes recebe alta hospitalar poucas horas após procedimentos considerados de baixa complexidade. Apesar desses avanços, os critérios tradicionalmente utilizados para alta permanecem fundamentados predominantemente em parâmetros fisiológicos, incluindo estabilidade hemodinâmica, recuperação motora, controle da dor e ausência de sintomas pós-operatórios significativos, enquanto a recuperação cognitiva raramente é incorporada aos protocolos de avaliação (NIHR NIHR Global Health Unit on Global Surgery; CovidSurg Collaborative, 2022; Rohi; Olofsson; Jakobsson, 2022). Nesse cenário, torna-se cada vez mais importante compreender se a recuperação clínica observada na alta corresponde efetivamente à recuperação funcional global do indivíduo, incluindo sua capacidade cognitiva (Rohi; Olofsson; Jakobsson, 2022).

As alterações cognitivas perioperatórias ainda são um desafio para a medicina perioperatória moderna. Embora tradicionalmente investigadas em pacientes idosos submetidos a cirurgias cardíacas ou procedimentos de grande porte, evidências recentes sugerem que alterações transitórias também podem ocorrer após cirurgias de pequeno porte e em indivíduos sem fatores de risco neurológicos evidentes (Amare; Mc Evoy; Smith, 2019; Au *et al.*, 2023). Essas manifestações podem comprometer domínios como atenção, memória, velocidade de processamento, aprendizagem e funções executivas, sendo frequentemente detectáveis apenas por meio de instrumentos neuropsicológicos padronizados (Brodier; Cibelli, 2020; Luo; Qiu; Wu, 2025; Miller *et al.*, 2018; Ramirez; Gan, 2023).

A relevância clínica dessas alterações torna-se particularmente evidente no momento da alta hospitalar. Nesse período, o paciente passa a ser responsável por compreender orientações médicas, administrar medicamentos, reconhecer sinais de alerta e tomar decisões relacionadas ao próprio cuidado. Consequentemente, mesmo déficits discretos e potencialmente transitórios podem comprometer a

autonomia funcional e a segurança durante o período pós-operatório imediato (Brodier; Cibelli, 2020; Rohi; Olofsson; Jakobsson, 2022).

As alterações cognitivas pós-operatórias podem manifestar-se de maneira sutil e subclínica. Sua investigação permanece desafiadora em razão da ausência de consenso sobre definições operacionais, critérios diagnósticos e métodos de avaliação. Revisões metodológicas demonstram considerável heterogeneidade entre os estudos publicados, dificultando comparações diretas e contribuindo para a inconsistência dos resultados disponíveis na literatura (Borchers *et al.*, 2021).

Em relação a fisiopatologia, essas alterações são tem etiologia multifatorial, resultantes da interação entre fatores inerentes ao paciente, ao procedimento cirúrgico e ao manejo anestésico (Liu *et al.*, 2023; Luo; Qiu; Wu, 2025; Safavynia; Goldstein, 2019). Diferentes mecanismos foram propostos relacionados a como tais episódios ocorrem, como processos inflamatórios sistêmicos decorrentes do trauma cirúrgico, ativação de vias de neuroinflamação, com quebra de barreira hematoencefálica, mudanças transitórias na conectividade neuronal, privação de sono, dor pós-operatória e os efeitos dos agentes anestésicos nos circuitos cerebrais envolvidos na cognição (Liu *et al.*, 2023; Luo; Qiu; Wu, 2025; Safavynia; Goldstein, 2019). Entre os mecanismos atualmente considerados, a neuroinflamação representa um dos principais (Safavynia; Goldstein, 2019). O trauma cirúrgico provoca respostas inflamatórias sistêmicas que podem causar alterações na permeabilidade da barreira hematoencefálica e ativação microglial, enquanto mediadores inflamatórios liberados do sistema nervoso central durante esses eventos podem comprometer o funcionamento dos circuitos neurais responsáveis pela atenção, memória, aprendizado e funções executivas (Brodier; Cibelli, 2020; Safavynia; Goldstein, 2019). Estudos demonstraram que vias inflamatórias específicas também podem influenciar algumas dessas alterações (Brodier; Cibelli, 2020; Safavynia; Goldstein, 2019). Outro fator a ser considerado é a manutenção da perfusão cerebral adequada durante o período intraoperatório, que representa um fator fundamental para a preservação da função cognitiva. Episódios de hipotensão arterial podem reduzir a pressão de perfusão cerebral, especialmente em pacientes com autorregulação cerebrovascular comprometida, favorecendo estados transitórios de hipofluxo cerebral. Embora a autorregulação seja capaz de manter o fluxo sanguíneo cerebral dentro de determinados limites pressóricos, reduções sustentadas da pressão arterial média podem ultrapassar essa capacidade

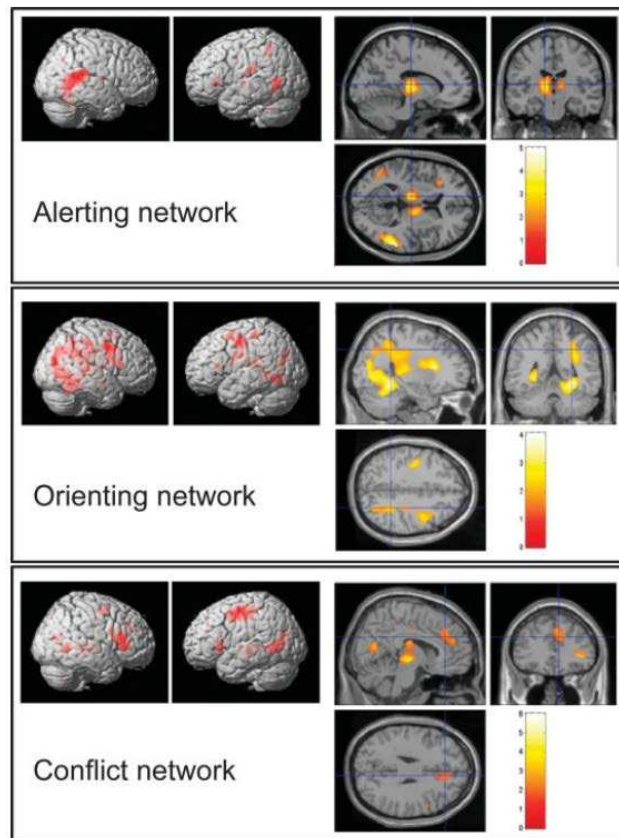
compensatória, resultando em diminuição da oferta de oxigênio e substratos energéticos ao tecido nervoso (Meng; Gelb, 2015). Essa condição pode desencadear alterações metabólicas, disfunção sináptica e ativação de mecanismos neuroinflamatórios, contribuindo para alterações cognitivas no período pós-operatório.

Nesse contexto, a atenção sustentada pode representar um dos domínios cognitivos mais sensíveis às alterações transitórias da perfusão cerebral, uma vez que depende da integridade funcional de circuitos frontoparietais altamente demandantes do ponto de vista metabólico. Assim, déficits observados na variabilidade do tempo de reação podem refletir, ao menos em parte, alterações funcionais decorrentes de episódios de hipoperfusão cerebral subclínica durante o período perioperatório.

Além disso, experimentos com uso de anestésicos inalatórios e venosos mostram que estes afetam a expressão gênica em diferentes partes do córtex pré-frontal humano, indicando que pode haver um impacto direto nos circuitos neurais relacionados à cognição (Flores *et al.*, 2017; Huels *et al.*, 2021; Kletecka *et al.*, 2019; Sanger *et al.*, 2014). A cognição envolve o processamento, aquisição e uso de informações sensoriais: atenção, memória, função executiva, linguagem, habilidades perceptuais e cognição social (Schmidt *et al.*, 2019, 2021).

Estudos de neuroimagem funcional demonstram que o desempenho atencional depende da integridade de circuitos frontoparietais, particularmente do córtex pré-frontal dorsolateral e do córtex parietal posterior. Essas regiões participam da manutenção do estado de alerta, da seleção de estímulos relevantes e do controle executivo do comportamento, sendo particularmente suscetíveis aos efeitos da inflamação sistêmica, do estresse fisiológico e de outras condições capazes de interferir na conectividade cerebral (Raz, 2004) (Figura 1).

Figura 1: Estudo de Raz (2004) de ressonância funcional evidenciando as principais redes atencionais



Alerting network: rede de alerta, *orienting network*: rede de orientação, *conflict network*: rede executiva.

Fonte: Figura extraída de Raz (2024).

Diversas condições clínicas e neurológicas associadas a alterações estruturais ou funcionais desses circuitos, incluindo dor crônica, transtornos neurodegenerativos, depressão, COVID-19 e situações de estresse físico ou mental, apresentam comprometimento predominante de componentes atencionais específicos (Filho *et al.*, 2022; Schmidt *et al.*, 2017; Simões *et al.*, 2018; van Duinkerken *et al.*, 2021). A observação consistente desse padrão em diferentes contextos sugere que a atenção, particularmente a atenção sustentada, constitui um dos sistemas cognitivos mais sensíveis a agressões biológicas transitórias ou persistentes (Filho *et al.*, 2022; Peters, 2006; Schmidt *et al.*, 2017, 2018, 2019; Simões; Carvalho; Schmidt, 2017; Simões *et al.*, 2018; van Duinkerken *et al.*, 2021).

A atenção é um sistema interconectado e consiste em velocidade de processamento, atenção focada, controle inibitório e atenção sustentada, com um significado: o desempenho constante do processamento contínuo durante um

processo monótono e rotineiro é relevante no estudo para alcançar resultados mesmo enquanto participamos de um processamento contínuo, mas repetitivo, memória de trabalho, resolução de problemas (Raz, 2004). De acordo com diferentes estudos clínicos, parece que mudanças na atenção sustentada podem ocorrer precocemente e preceder manifestações cognitivas mais amplas, podendo, portanto, ser vistas como um biomarcador importante de vulnerabilidade neurocognitiva (Filho *et al.*, 2022; Peters, 2006; Simões; Carvalho; Schmidt, 2017; Schmidt *et al.*, 2017, 2018, 2019; Simões *et al.*, 2018; van Duinkerken, 2021). Além disso, condições pós-operatórias como dor, fadiga, privação de sono, estresse fisiológico e reorganização da rede neural após anestesia geral têm influências diretas nos mecanismos de atenção, onde mudanças cognitivas após mudanças cognitivas perioperatórias poderiam ocorrer inicialmente através da perda de atenção sustentada (Filho *et al.*, 2022; Peters, 2006; Schmidt *et al.*, 2017, 2018, 2019; Simões; Carvalho; Schmidt, 2017; Simões *et al.*, 2018; van Duinkerken, 2021).

Nesse contexto, surgiu a hipótese de que diferentes agentes anestésicos poderiam influenciar distintamente a recuperação cognitiva pós-operatória. O propofol tem sido investigado por suas propriedades anti-inflamatórias, antioxidantes e imunomoduladoras (Inada; Hirota; Shingu, 2015; Irwin *et al.*, 2020). Em contraste, o sevoflurano tem sido associado a mecanismos relacionados à neuroinflamação, disfunção mitocondrial, apoptose neuronal e alterações na plasticidade sináptica em estudos experimentais (Wang *et al.*, 2021; Zhou *et al.*, 2023). Esses achados forneceram suporte biológico para a hipótese de que a anestesia intravenosa total baseada em propofol poderia oferecer vantagens sobre a anestesia inalatória baseada em sevoflurano na preservação da função cognitiva. No entanto, apesar da plausibilidade biológica dessas hipóteses, os resultados clínicos permanecem inconclusivos (Miller *et al.*, 2018). Ensaio clínicos randomizados, revisões sistemáticas e meta-análises não demonstraram superioridade consistente de uma técnica anestésica sobre a outra em relação aos desfechos cognitivos pós-operatórios (Chen *et al.*, 2016, 2022; Guo *et al.*, 2020; Kletecka *et al.*, 2019; Negrini *et al.*, 2022; Ramirez; Gan, 2023). As observações experimentais e clínicas divergentes fornecem evidências de que o efeito fisiopatológico das mudanças neurocognitivas perioperatórias é complexo e provavelmente é influenciado por múltiplos componentes biológicos, cirúrgicos e anestésicos que ocorrem (Brodier; Cibelli, 2020).

Durante o trabalho de desenho deste projeto, exploramos uma revisão narrativa da literatura sobre o efeito da técnica anestésica nos desfechos cognitivos pós-operatórios em profundidade neste estudo. Os autores publicaram o artigo *Implicações da Técnica Anestésica nas Alterações Cognitivas Pós-operatórias: Propofol versus Sevoflurano*, nos *Cadernos Brasileiros de Medicina*, em 2025. Tornou-se evidente após uma pesquisa detalhada da literatura que não há superioridade geral no desenvolvimento clínico das duas técnicas, apesar das diferenças biológicas descritas para tratamentos clínicos com uma delas (Guo *et al.*, 2020; Inada; Hirota; Shingu, 2015; Irwin *et al.*, 2020; Liu *et al.*, 2023; Luo; Qiu; Wu, 2025; Miller *et al.*, 2018; Negrini *et al.*, 2022).

Com base nesses resultados, um protocolo prospectivo foi desenvolvido no Registro Brasileiro de Ensaios Clínicos (ReBEC - RBR-6xhp399; UTN U1111-1295-3640) e aprovado pelo comitê de ética em pesquisa da Universidade Federal do Estado do Rio de Janeiro (CAAE 54581221.0.0000.5258).

Considerando a relevância da atenção sustentada, já citada, como possível marcador precoce de vulnerabilidade neurocognitiva, torna-se necessária a utilização de instrumentos capazes de avaliá-la objetivamente. Nesse contexto, o *Computerized Visual Attention Test* (CVAT) foi utilizado para mensurar velocidade de resposta, atenção focada, controle inibitório e atenção sustentada por meio de uma tarefa breve e padronizada (Borchers *et al.*, 2021; Filho *et al.*, 2022). Entre seus parâmetros, destaca-se a Variabilidade do Tempo de Reação (*Variability of Reaction Time* - VRT), considerada uma medida objetiva da estabilidade do desempenho atencional ao longo do tempo. O aumento da VRT reflete lapsos atencionais transitórios e tem sido proposto como potencial biomarcador de vulnerabilidade neurocognitiva em diferentes condições clínicas (Simões; Carvalho; Schmidt, 2017; van Duinkerken, 2021).

O presente trabalho deriva de um protocolo prospectivo mais amplo registrado previamente no Registro Brasileiro de Ensaios Clínicos (ReBEC - RBR-6xhp399; UTN U1111-1295-3640), concebido para investigar diferentes aspectos das alterações neurocognitivas associadas ao período perioperatório. O projeto original contemplava uma abordagem mais abrangente, incluindo desfechos clínicos, neuropsicológicos e biomarcadores biológicos. A presente tese corresponde a uma análise específica desse protocolo, direcionada à investigação da recuperação cognitiva após cirurgias de pequeno porte e à caracterização da atenção sustentada

como potencial marcador de vulnerabilidade neurocognitiva no momento da alta hospitalar. Dessa forma, os resultados aqui apresentados devem ser compreendidos como parte de um programa de pesquisa mais amplo, cujas demais análises serão objeto de futuras publicações. Foi nesse contexto que a presente tese foi desenvolvida.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Investigar a ocorrência de alterações cognitivas após cirurgias de pequeno porte sob anestesia geral, com ênfase nos mecanismos atencionais, e avaliar sua relevância para a recuperação pós-operatória e para a segurança da alta hospitalar.

3.2 OBJETIVOS ESPECÍFICOS

3.2.1 Objetivo Específico 1

Revisão narrativa da literatura sobre o efeito da técnica anestésica nos desfechos cognitivos pós-operatórios.

3.2.2 Objetivo Específico 2

Caracterizar o desempenho neuropsicológico de pacientes submetidos à colecistectomia videolaparoscópica eletiva sob anestesia geral por meio de instrumentos padronizados de avaliação cognitiva que incluem CVAT, COWAT e SDMT.

3.2.3 Objetivo Específico 3

Comparar os efeitos da anestesia venosa total baseada em propofol e da anestesia inalatória baseada em sevoflurano sobre os desfechos neuropsicológicos no período pós-operatório.

3.2.4 Objetivo Específico 4

Avaliar a evolução temporal do desempenho cognitivo no período pós-operatório imediato (D1) e durante o seguimento em 15 (D15) e 45 dias (D45) após a cirurgia.

3.2.5 Objetivo Específico 5

Contribuir para a compreensão dos mecanismos envolvidos na recuperação cognitiva após cirurgias de pequeno porte, integrando os resultados desta investigação às análises futuras previstas no protocolo original registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC - RBR-6xhp399; UTN U1111-1295-3640).

4 MATERIAIS E MÉTODOS

Esta tese deriva de uma análise prospectiva previamente planejada dentro de protocolo de pesquisa registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC - RBR-6xhp399; UTN U1111-1295-3640) e aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal do Estado do Rio de Janeiro (CAAE 54581221.0.0000.5258). O protocolo original foi desenvolvido para investigar múltiplos aspectos da recuperação perioperatória após anestesia geral, incluindo desfechos neuropsicológicos, clínicos e laboratoriais. A presente investigação concentra-se especificamente na avaliação das alterações cognitivas pós-operatórias e em sua evolução temporal, constituindo uma das análises previstas no projeto original. As avaliações foram realizadas no período pré-operatório (D0), na alta hospitalar (D1), 15 dias após o procedimento (D15) e 45 dias após a cirurgia (D45).

4.1 AVALIAÇÃO NEUROPSICOLÓGICA

A avaliação cognitiva foi realizada por meio de uma bateria composta por instrumentos validados para investigação de diferentes domínios neuropsicológicos.

4.1.1 Computerized Visual Attention Test (CVAT)

O Computerized Visual Attention Test (CVAT) foi desenvolvido por Sérgio Schmidt e colaboradores com o objetivo de avaliar, de forma objetiva e independente, diferentes componentes da atenção por meio de uma tarefa computadorizada breve, padronizada e de fácil aplicação. O instrumento foi concebido a partir do paradigma neuropsicológico *go/no-go*, amplamente utilizado para investigação dos mecanismos de atenção e controle executivo, permitindo a dissociação de subdomínios atencionais frequentemente avaliados de forma conjunta em testes convencionais (Schmidt, 2004) (Figura 2).

Figura 2: Teste computadorizado de atenção visual



(I) Tela ilustrativa de instruções iniciais. (II) Estímulo alvo (estrela), diante do qual o participante deve pressionar a barra de espaço. (III) Estímulo não-alvo (losango) diante do qual o participante deve ater-se de pressionar a barra de espaço.

Durante a realização do teste, estímulos visuais são apresentados sequencialmente em uma tela de computador. O participante deve responder rapidamente sempre que um estímulo-alvo é apresentado (*go*) e inibir a resposta diante de estímulos não alvo (*no-go*). Embora a tarefa seja simples, seu desempenho depende da interação de múltiplos sistemas cognitivos relacionados à vigilância, atenção focada, atenção sustentada, velocidade de processamento e controle inibitório (Filho *et al.*, 2022; Schmidt *et al.*, 2019; van Duinkerken, 2021).

Estudos de validação neuropsicológica e de ressonância magnética funcional confirmaram a associação entre o desempenho no CVAT e o funcionamento dos circuitos frontoparietais, que fornecem atenção, monitoramento de resposta e controle executivo, particularmente no córtex pré-frontal dorsolateral e no córtex parietal posterior (Petersen; Posner, 2012; Raz, 2004). O CVAT fornece quatro medidas independentes (Simões *et al.*, 2018).

4.1.1.1 Tempo de Reação (RT)

O tempo de reação é o intervalo entre a apresentação do estímulo-alvo e a resposta do participante. Ele representa a velocidade de processamento de informações e quão rapidamente o cérebro inteiro aprende, percebe e reage a estímulos ambientais. Um RT maior pode envolver fadiga cognitiva ou baixo nível de alerta associado a uma atividade de processamento cerebral mais lenta.

4.1.1.2 Variabilidade do Tempo de Reação (VTR)

A variabilidade do tempo de reação é a flutuação dos tempos de resposta ao longo da tarefa. Enquanto o RT é apenas uma escala de velocidade de resposta (ou seja, a velocidade média de resposta), o VRT avalia a consistência do desempenho cognitivo ao longo do teste. Valores mais altos indicam uma maior instabilidade atencional, pois você tem períodos de desempenho adequado e há curtos lapsos de atenção. Atualmente, o VRT é considerado uma das medidas mais sensíveis de atenção sustentada e tem sido sugerido como um possível biomarcador comportamental de vulnerabilidade neurocognitiva (Filho *et al.*, 2022; Simões *et al.*, 2018).

4.1.1.3 Erros de Omissão (EO)

Erros de omissão ocorrem quando o participante não responde a um estímulo específico. Consideramos que esses são erros de vigilância, falta de alerta e déficit de atenção porque muitas vezes não estamos preparados para prestar muita atenção e gerenciar o que funcionará. Por essa razão, em teoria e função, esses são os erros que experimentamos no tempo quando alguns componentes do que é informação relevante não são abordados por nossos cérebros de forma eficaz. É frequentemente a presença de uma ausência de consciência, sonolência, fadiga, desempenho reduzido e diminuição nos níveis de concentração que resulta em uma maior probabilidade de erro por omissão.

4.1.1.4 Erros de Comissão (CE)

Erros de comissão ocorrem quando o usuário reage de forma inadequada a estímulos não-alvo. Essa condição está principalmente ligada à inibição e controle de respostas impulsivas (Simões *et al.*, 2018). Erros de comissão indicam a falha do controlador em capturar e parar. Eles podem estar associados a comportamento impulsivo e a um controle executivo prejudicado. Um dos aspectos críticos do CVAT é a capacidade de separar vários componentes da atenção, atualmente sendo

combinados em outros testes neuropsicológicos (Simões *et al.*, 2018). Assim, este teste nos permite identificar mais rapidamente quais aspectos da atenção estão inibidos em um determinado conjunto de condições clínicas.

Desde seu desenvolvimento, o CVAT tem sido extensivamente trabalhado pelo grupo de pesquisa de Sérgio Schmidt e seus colaboradores, com descobertas que se mostraram significativas e foram aplicadas em áreas clínicas e experimentais. Numerosos estudos em diferentes países revelaram em pessoas com transtorno do déficit de atenção e hiperatividade, comprometimento cognitivo leve com doença de Alzheimer, distúrbios do sono, Fibromialgia, doença renal crônica, fadiga (COVID-19) e outros distúrbios de vulnerabilidade neurocognitiva (Eelco van Duinkerken, 2021) (Abramovicz *et al.*, 2025; Filho *et al.*, 2022; Simões; Carvalho; Schmidt, 2017). Além disso, estudos de validação neuropsicológica, análise normativa e estudos de neuroimagem funcional estabeleceram que o CVAT é uma maneira realista de avaliar mecanismos de atenção (Petersen; Posner, 2012; Raz, 2004). Na presente investigação, optou-se pela versão de 5 minutos do teste por representar o melhor equilíbrio entre robustez psicométrica e viabilidade clínica. Embora versões mais longas possam proporcionar discretos ganhos de precisão, sua duração aumenta a fadiga e dificulta a aplicação no período perioperatório. Por outro lado, a versão ultrabreve de 90 segundos foi desenvolvida principalmente para rastreamento rápido, apresentando menor número de estímulos e, conseqüentemente, menor precisão na estimativa dos parâmetros atencionais, particularmente da variabilidade do tempo de reação, cuja confiabilidade depende de um número suficiente de observações. Dessa forma, a versão de 5 minutos foi considerada a mais adequada para detectar alterações cognitivas sutis no contexto da recuperação anestésica, preservando a sensibilidade do instrumento sem comprometer sua factibilidade no momento da alta hospitalar.

Em ambientes perioperatórios, no entanto, o CVAT ainda tem pouca utilização. De acordo com o que sabemos até agora, a presente pesquisa é de longe uma das primeiras aplicações sistemáticas do instrumento no tratamento de alterações cognitivas após cirurgia e anestesia geral, e pioneira e original em seu uso como meio de testar a recuperação cognitiva com atenção sustentada na alta hospitalar. Isso também foi para desenvolver a aplicação do teste à medicina perioperatória, que ainda é muito nova e, portanto, fomos capazes de investigar mudanças cognitivas sutis que não são encontradas por métodos convencionais

(Borchers *et al.*, 2021). Como a atenção sustentada seria reconhecida como um dos sistemas cognitivos mais sensíveis a mudanças rápidas no corpo durante um estado humano (ou seja, estados fisiológicos de longo prazo e agudos, como a reativação emocional da resposta corporal através da ansiedade e/ou resposta ao estresse físico e inflamação) e porque essas mudanças fisiológicas afetam a estabilidade atencional, o VRT foi estudado como seus maiores parâmetros cognitivos nesta tese. Como resultado, o CVAT é considerado até agora não apenas como um método de diagnóstico neuropsicológico, mas também como uma ferramenta para a recuperação pós-operatória na alta hospitalar e para avaliar o papel da atenção sustentada como um marcador de prontidão funcional como uma avaliação objetiva do resultado da recuperação após cirurgia e recuperação da anestesia.

4.1.2 Controlled Oral Word Association Test (COWAT)

O COWAT tem sido usado para medir a fluência verbal fonêmica e aspectos executivos associados à busca lexical, organização estratégica da informação e controle cognitivo (Ross *et al.*, 2007). Sua invenção foi resultado de Arthur Lester Benton, um neurologista e neuropsicólogo que foi considerado um dos pioneiros mais influentes na pesquisa neuropsicológica clínica com impacto seminal em técnicas e ferramentas cognitivas padronizadas (Ruff *et al.*, 1996). Este teste requer o processamento oral de tantas palavras quanto possível começando com (as letras certas) em intervalos de um minuto para cada letra individual, ou seja, existem certas regras para não usar muitas palavras e diferentes inflexões da mesma palavra quando você o executa. É baseado em múltiplos domínios, a saber, acesso lexical, memória semântica, velocidade de recuperação verbal, flexibilidade cognitiva, monitoramento de resposta e controle executivo. Portanto, é bem conhecido que o COWAT é uma medida sensível da integridade do sistema frontal, e há um papel influente que ele desempenha quando tentamos entender as funções executivas de todos os seres humanos porque ele não fornece informações suficientes pela primeira vez sem motivo para conhecer suas competências (Benton, 1968).

4.1.3 Symbol Digit Modalities Test (SDMT)

O SDMT foi desenvolvido por Aaron Smith, um neuropsicólogo americano, estabelecido pela primeira vez em 1968 e é destinado a fins de detecção de comprometimento cerebral e de aprendizagem (Strober *et al.*, 2019). O teste foi desenvolvido como uma adaptação reversa do subteste de Símbolos e Dígitos da Escala de Inteligência Wechsler para fornecer um marcador simples e rápido (ou melhor, responsivo) do funcionamento cognitivo (Pereira; Costa; Cerqueira, 2015). Agora é amplamente utilizado como uma das abordagens neuropsicológicas clínicas mais estudadas e pesquisadas para examinar as mudanças cerebrais associadas a condições médicas neurológicas, psiquiátricas e sistêmicas. O SDMT é uma tarefa de substituição de símbolo-número na qual os participantes são solicitados a usar uma chave com 9 símbolos, bem como números de 1 a 9. A partir disso, eles devem identificar o maior número possível de associações corretas dentro de um determinado intervalo de tempo. A tarefa exige processamento rápido e simultâneo de informações visuais, atenção sustentada, rastreamento visual, memória operacional e coordenação visuomotora (Pereira; Costa; Cerqueira, 2015; Strober *et al.*, 2019).

Por envolver múltiplos processos cognitivos de forma integrada, o SDMT é considerado uma das medidas mais sensíveis da velocidade de processamento cognitivo. Seu desempenho também reflete aspectos da eficiência atencional, da flexibilidade mental e da integração visuomotora, sendo particularmente útil para a detecção de alterações cognitivas sutis. Em razão de sua elevada sensibilidade, ampla utilização internacional e facilidade de aplicação, o SDMT foi incluído na presente pesquisa como medida complementar da eficiência cognitiva global e da velocidade de processamento das informações (Pereira; Costa; Cerqueira, 2015; Strober *et al.*, 2019).

4.1.4 Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

Todos os participantes randomizados foram submetidos à avaliação sistemática por meio do Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). O CAM-ICU é um instrumento validado internacionalmente para

rastreamento de delirium em pacientes hospitalizados, incluindo indivíduos submetidos a procedimentos cirúrgicos e pacientes em unidades de terapia intensiva (Miranda *et al.*, 2023). O método é baseado em quatro características básicas: início agudo ou curso flutuante de alterações mentais, déficit de atenção, nível de consciência alterado e pensamento desorganizado. Neste caso, o diagnóstico de delirium é feito quando há fortes alterações do estado mental e déficit de atenção associados ao nível de consciência alterado ou pensamento desorganizado (Miranda *et al.*, 2023). O CAM-ICU permitiu que o delirium não fosse mais o fator de confusão para a compreensão dos resultados neuropsicológicos, com as alterações cognitivas sendo interpretadas não como sintomas de uma doença em si, mas como um déficit sutil observado por certos testes cognitivos, mas como parte de uma condição neuropsiquiátrica aguda.

4.2 SELEÇÃO DOS PACIENTES

Os pacientes foram selecionados conforme critérios descritos no quadro 1.

Quadro 1: Critérios de inclusão e exclusão dos participantes do estudo

Idade ≥ 18 anos	ASA III ou IV
Pacientes submetidos à colecistectomia videolaparoscópica eletiva	Cirurgia de urgência ou emergência
Estado físico ASA I ou II	Doença neurológica ou psiquiátrica prévia
Consentimento Livre e Esclarecido assinado	Uso crônico de opioides, benzodiazepínicos ou antipsicóticos
Capacidade de compreender e realizar os testes neuropsicológicos	Déficits visuais ou auditivos que impedissem a realização dos testes

5 RESULTADOS

5.1 ARTIGO 1 REFERENTE AO OBJETIVO ESPECÍFICO 1

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Implicações da Técnica Anestésica nas Alterações Cognitivas Pós-operatórias: Propofol versus Sevoflurano. Revisão Narrativa

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Implicações da Técnica Anestésica nas Alterações Cognitivas Pós-operatórias: Propofol versus Sevoflurano. Revisão Narrativa

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Resumo

As alterações cognitivas pós-operatórias são complicações frequentes em pacientes idosos. Esta revisão narrativa analisa as implicações da técnica anestésica nas alterações cognitivas pós-operatórias, com foco na comparação entre anestesia venosa total com propofol e anestesia inalatória com sevoflurano. Evidências experimentais e clínicas sugerem possível vantagem do propofol na preservação cognitiva precoce, enquanto diferenças tardias mostram-se inconsistentes. A profundidade anestésica e o manejo perioperatório global parecem exercer influência mais relevante do que a escolha isolada do agente.

Palavras-chave: anestesia geral, propofol, sevoflurano, delírio pós-operatório, distúrbios cognitivos pós-operatórios.

Implications of Anaesthetic Technique on Postoperative Cognitive Changes: Propofol versus Sevoflurane. A Narrative Review

Abstract

Postoperative cognitive disorders are common complications after surgery, particularly in elderly patients. This narrative review discusses the impact of anesthetic technique on postoperative cognitive outcomes, focusing on propofol-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia. Experimental and clinical evidence suggests a potential benefit of propofol for early cognitive preservation, whereas long-term differences are inconsistent.

Keywords: general anesthesia, propofol, sevoflurane, postoperative delirium, perioperative neurocognitive disorders.

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1. Introdução Geral

As alterações cognitivas pós-operatórias são manifestações clínicas de apresentação variável, que envolvem um ou mais domínios cognitivos como memória, atenção, função executiva e linguagem¹. Tem maior prevalência em idosos, e em procedimentos de alta complexidade². Portanto, no cenário atual, passa a ter maior relevância diante do envelhecimento progressivo da população e do aumento da complexidade dos procedimentos cirúrgicos. Nesse contexto, o *delirium* pós-operatório e as alterações cognitivas pós-operatórias podem ser mensuradas por testes neuropsicológicos comparativos com o basal do indivíduo, podem apresentar elevada prevalência e impacto prognóstico do paciente^{1,2}.

Essas alterações cognitivas não se limitam a manifestações transitórias sem relevância clínica. Diversos estudos demonstram associação entre alterações cognitivas pós-operatórias e prolongamento do tempo de internação hospitalar, aumento do risco de complicações infecciosas, perda de independência funcional e aumento da mortalidade em curto e longo prazo^{2,3}. Além disso, o impacto sobre a qualidade de vida do paciente e de seus cuidadores confere a esses distúrbios importância que extrapola o período perioperatório imediato, assumindo relevância em saúde pública.

Historicamente, o termo Disfunção Cognitiva Pós-operatória (DCPO) foi utilizado para descrever o declínio cognitivo observado após procedimentos cirúrgicos. Entretanto, a ausência de critérios diagnósticos uniformes, a variabilidade nos instrumentos neuropsicológicos empregados e a inconsistência temporal das avaliações dificultaram a interpretação dos resultados e a comparação entre estudos^{1,2}.

A fisiopatologia das alterações cognitivas pós-operatórias é reconhecidamente multifatorial, envolvendo a interação complexa entre fatores relacionados ao paciente, ao procedimento cirúrgico e ao manejo anestésico e perioperatório³. Entre os fatores relacionados ao paciente, eles contribuem para maior vulnerabilidade cerebral frente aos estressores perioperatórios, destacam-se idade avançada, fragilidade, baixa reserva cognitiva, presença de comorbidades cardiovasculares e metabólicas, distúrbios neuropsiquiátricos prévios e alterações estruturais ou funcionais do sistema nervoso central^{2,3}.

Do ponto de vista cirúrgico, a magnitude do trauma tecidual, a duração do procedimento, a perda sanguínea e a resposta inflamatória sistêmica desempenham papel central na gênese das alterações cognitivas³. Procedimentos de maior porte, particularmente aqueles associados a resposta inflamatória intensa, como cirurgias cardíacas com circulação extracorpórea, apresentam maior risco de *delirium* e declínio cognitivo³.

Nesse cenário complexo, o manejo anestésico surge como um potencial modulador dos desfechos neurocognitivos. A anestesia geral, em particular, tem sido amplamente investigada devido à sua capacidade de interferir diretamente na atividade neuronal, na

conectividade cortical, na hemodinâmica cerebral e na resposta inflamatória sistêmica³. Diferentes agentes anestésicos apresentam perfis farmacodinâmicos e neurofisiológicos distintos, o que levanta a hipótese de que a escolha da técnica anestésica possa influenciar a ocorrência e a gravidade das alterações cognitivas pós-operatórias³.

Neste contexto, a comparação entre anestesia venosa total (TIVA) com propofol e anestesia inalatória com sevoflurano assume especial relevância clínica, uma vez que ambas as técnicas são amplamente utilizadas na prática anestésica contemporânea. O propofol é um agente hipnótico intravenoso com ação predominantemente GABAérgica, caracterizado por rápida indução e despertar previsível, além de propriedades anti-inflamatórias e antioxidantes descritas em estudos experimentais⁴, que nos permite a hipótese de uma ação protetora para alterações cognitivas pós-operatórias. Em contrapartida, o sevoflurano é um anestésico inalatório halogenado amplamente utilizado, com perfil favorável de estabilidade hemodinâmica e rápida eliminação pulmonar, características que o tornam bem indicado em diversos contextos clínicos, principalmente em cirurgias de curta duração⁴.

Entretanto, evidências experimentais sugerem que a exposição a anestésicos voláteis, como sevoflurano, pode intensificar a neuroinflamação, promover disfunção sináptica e induzir alterações cognitivas persistentes, especialmente em cérebros envelhecidos^{5,6}. Essas observações levantam questionamentos sobre a possível relação entre uso de sevoflurano e aumento do risco de alterações cognitivas pós-operatórias, e reforçam a necessidade de análise crítica da literatura disponível.

Apesar da plausibilidade biológica para diferenças entre propofol e sevoflurano, os resultados dos estudos clínicos permanecem heterogêneos e, por vezes, conflitantes. Diferenças metodológicas importantes, incluindo variação nos instrumentos de avaliação cognitiva, nos critérios diagnósticos adotados, nos tempos de seguimento e no controle de fatores de confusão, dificultam a interpretação dos achados e a extrapolação para a prática clínica. Assim, torna-se essencial uma abordagem integrada que considere não apenas a escolha do agente anestésico, mas também o contexto clínico e o manejo perioperatório global^{7,8}.

2. Metodologia

Trata-se de uma revisão narrativa de literatura que busca responder a seguinte pergunta norteadora: "A técnica anestésica influencia as alterações cognitivas pós-operatórias? Uma comparação entre propofol e sevoflurano".

A revisão narrativa é caracterizada por uma análise crítica da literatura do ponto de vista teórico ou contextual, sendo adequada para a proposta da pesquisa, haja vista que para a aplicação do método não é necessário estabelecer rígidos critérios ou sistematização no desenvolvimento da pesquisa, sendo possível a discussão de novos temas e caminhos teórico-metodo-

lógicos a partir de fontes documentais.

Para a realização desse levantamento bibliográfico, foram consultadas referências sobre a temática da disfunção cognitiva pós-operatória e uso de propofol ou sevoflurano, nas bases de dados SciELO, PubMed e Google Acadêmico. O período de referência do levantamento foi de outubro de 2020 a outubro de 2025. Foram utilizados os seguintes Descritores em Ciências da Saúde (DeCS): cognitive outcomes, propofol, sevoflurane, e seus respectivos correspondentes em português, combinados entre si por operadores booleanos "AND" e "OR".

Os dados coletados para a seleção dos artigos analisados neste estudo atenderam aos seguintes critérios de inclusão: tratar-se de artigo original, disponibilizado na íntegra (*free full text*), no idioma de língua portuguesa ou inglesa, cujo objeto de estudo fosse de interesse desta revisão narrativa e que estivesse disponível em formato eletrônico na base de dados, publicado nos últimos 5 anos. Já os critérios de exclusão foram: artigos de relato de experiência, opinião de autoridades e relatórios de comitês de especialistas, editoriais e artigos que, embora abordassem alterações cognitivas, tratassem de situações relacionadas a doenças ou medicamentos específicos.

Após a seleção dos artigos e aplicação dos critérios em questão, as publicações foram revisadas e catalogadas observando-se o enfoque mencionado anteriormente. Os artigos foram catalogados em planilha no software Excel[®] conforme o ano de publicação, tipo de estudo e principais conclusões para facilitar a compreensão da produção científica e sistematização dos achados. Como a revisão é de natureza descritiva, os dados extraídos dos estudos selecionados não foram combinados estatisticamente, sobretudo devido à heterogeneidade metodológica e dos desenhos dos estudos envolvidos.

Por fim, considerando que o tipo de estudo não envolve seres humanos, enfatiza-se que não há a exigência de submissão ao Comitê de Ética em Pesquisa (CEP), conforme interpretação da Resolução CNS nº 466/2012 que aprova as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos.

3. Desenvolvimento

3.1. Distúrbios neurocognitivos perioperatórios: conceitos atuais

3.1.1. Delírium pós-operatório

O delírium pós-operatório é caracterizado por distúrbio agudo da atenção e da consciência, com curso flutuante e alteração da cognição, geralmente manifestado nos primeiros dias após a cirurgia. Trata-se de condição altamente prevalente em pacientes idosos e criticamente enfermos, sendo considerada um marcador de vulnerabilidade cerebral e de reserva cognitiva reduzida¹².

Clinicamente, o delírium pode apresentar-se sob formas hiperativa, hipoativa ou mista, sendo a forma hipoativa frequentemente subdiagnosticada. A identificação precoce do delírium é fundamental, uma

vez que sua ocorrência associa-se a piores desfechos clínicos, incluindo aumento da mortalidade, prolongamento da internação hospitalar e maior risco de institucionalização².

3.1.2. Declínio cognitivo pós-operatório

O declínio cognitivo pós-operatório refere-se à piora mensurável do desempenho cognitivo em relação ao estado basal, detectável por testes neuropsicológicos padronizados. Diferentemente do delírium, trata-se de condição geralmente mais sutil, que pode persistir por semanas ou meses após o procedimento cirúrgico. A incorporação do declínio cognitivo ao conceito mais amplo de alterações cognitivas pós-operatórias permitiu reconhecer a continuidade entre diferentes manifestações de disfunção cognitiva associadas ao período perioperatório. Essa abordagem enfatiza a importância de avaliações cognitivas sistemáticas e longitudinalmente estruturadas, especialmente em populações de alto risco¹.

3.1.3. Limitações conceituais e metodológicas

Apesar dos avanços conceituais, persistem limitações metodológicas relevantes nos estudos sobre alterações cognitivas pós-operatórias. A heterogeneidade dos instrumentos neuropsicológicos utilizados, a variabilidade nos tempos de avaliação e a ausência de critérios diagnósticos uniformes em estudos mais antigos dificultam a comparação direta entre os resultados³. Essas limitações devem ser consideradas na interpretação crítica da literatura.

3.2. Bases fisiopatológicas dos distúrbios neurocognitivos perioperatórios

A fisiopatologia das alterações cognitivas pós-operatórias é complexa e envolve múltiplos mecanismos inter-relacionados. Evidências acumuladas indicam que a neuroinflamação desempenha papel central nesse processo. O trauma cirúrgico desencadeia resposta inflamatória sistêmica caracterizada pela liberação de citocinas pró-inflamatórias, ativação do sistema imune inato e aumento da permeabilidade da barreira hematoencefálica⁶.

Esses mediadores inflamatórios alcançam o sistema nervoso central, promovendo ativação microglial e disfunção sináptica. A ativação microglial resulta na liberação local de citocinas, espécies reativas de oxigênio e óxido nítrico, comprometendo a plasticidade sináptica e a integridade de redes neurais envolvidas em atenção, memória e funções executivas, particularmente no córtex pré-frontal e no hipocampo^{6,7}.

Além da neuroinflamação, outros mecanismos têm sido implicados na gênese das alterações cognitivas pós-operatórias, incluindo estresse oxidativo, disfunção mitocondrial, alterações nos sistemas colinérgico e dopaminérgico e perturbações do ritmo sono-vigília. A anestesia geral pode interagir com esses mecanismos, modulando a atividade neuronal, a hemodinâmica cerebral e a resposta inflamatória sistêmica^{3,7}.

Nesse contexto, diferenças farmacológicas entre agen-

tes anestésicos podem resultar em efeitos distintos sobre os processos fisiopatológicos subjacentes as alterações cognitivas pós-operatórias, fornecendo base teórica para a investigação comparativa entre TIVA com propofol e anestesia inalatória com sevoflurano.

3.3. Evidência experimental e translacional

Modelos animais têm sido amplamente utilizados para investigar os efeitos dos anestésicos sobre a função cognitiva e os mecanismos subjacentes as alterações cognitivas pós-operatórias. Estudos experimentais demonstram que a exposição a anestésicos voláteis, incluindo o sevoflurano, pode intensificar a ativação microglial, aumentar a expressão de citocinas pró-inflamatórias e promover apoptose neuronal, especialmente em animais envelhecidos^{5,6}.

Huang et al. demonstraram que ratos idosos expostos ao sevoflurano apresentaram pior desempenho em testes de memória e aprendizado, associado a aumento significativo de marcadores inflamatórios cerebrais^{4,5}. Achados semelhantes foram descritos em outros modelos experimentais, reforçando a associação entre anestesia volátil, neuroinflamação e disfunção cognitiva.

Em contraste, o propofol tem sido associado à atenuação da resposta inflamatória cerebral em modelos experimentais. Estudos demonstram redução da ativação microglial, menor liberação de citocinas pró-inflamatórias e preservação da função sináptica em animais anestesiados com propofol^{4,7}. Esses achados sustentam a hipótese de potencial efeito neuroprotetor do propofol.

3.4. Evidência clínica em cirurgias não cardíacas

Ensaio clínico randomizado e estudos observacionais em cirurgias não cardíacas têm investigado a associação entre técnica anestésica e desfechos neurocognitivos, particularmente em populações idosas. Diversos estudos sugerem que a TIVA com propofol pode estar associada a menor incidência de declínio cognitivo precoce quando comparada à anestesia inalatória com sevoflurano^{4,8}.

Geng et al. avaliaram pacientes idosos submetidos a colecistectomia laparoscópica e observaram menor incidência de declínio cognitivo nos primeiros dias pós-operatórios em pacientes anestesiados com propofol, além de menores níveis plasmáticos de S100β, um biomarcador de lesão neuronal⁴. Esses achados sugerem possível benefício cognitivo precoce associado à TIVA.

Meta-análises e revisões sistemáticas, incluindo a revisão Cochrane, corroboram parcialmente esses resultados, indicando redução modesta do risco de alterações cognitivas pós-operatórias precoce em cirurgias não cardíacas com o uso de TIVA^{8,9}. Contudo, a elevada heterogeneidade metodológica observada entre os estudos limita a robustez dessas conclusões.

Apesar dos resultados favoráveis observados em alguns estudos quanto à proteção cognitiva precoce com o uso de propofol, é fundamental interpretar

esses achados à luz de limitações metodológicas relevantes. Muitos ensaios clínicos apresentam amostras relativamente pequenas, curto período de seguimento e diversidade nos instrumentos utilizados para avaliação cognitiva, o que dificulta comparações diretas e a generalização dos resultados. Além disso, a definição de declínio cognitivo varia substancialmente entre os estudos, podendo influenciar a magnitude dos efeitos observados^{3,8}.

Outro aspecto relevante é o momento da avaliação cognitiva. Evidências sugerem que diferenças entre propofol e sevoflurano tendem a ser mais evidentes no pós-operatório imediato, geralmente nos primeiros dias após a cirurgia. Quando avaliações são realizadas em períodos mais tardios, como semanas ou meses após o procedimento, as diferenças frequentemente desaparecem, sugerindo que o impacto da técnica anestésica sobre a cognição pode ser transitório^{8,9}.

Revisões sistemáticas recentes e meta-análises reforçam essa interpretação, indicando que, embora a anestesia venosa total possa estar associada a menor incidência de alterações cognitivas pós-operatórias precoce em cirurgias não cardíacas, não há evidência robusta de benefício sustentado a longo prazo⁹. Esses achados sugerem que a técnica anestésica, embora relevante, representa apenas um dos múltiplos fatores envolvidos evolução cognitiva pós-operatória.

Além disso, estudos observacionais destacam a influência de fatores perioperatórios concomitantes, como controle inadequado da dor, uso excessivo de opioides e benzodiazepínicos, hipotensão intraoperatória e distúrbios do sono, os quais podem exercer impacto mais pronunciado sobre os desfechos cognitivos do que a escolha isolada do agente anestésico³. Assim, a interpretação dos benefícios potenciais do propofol deve considerar o contexto do manejo perioperatório global.

3.5. Evidência clínica em cirurgia cardíaca

A cirurgia cardíaca representa um cenário singular no estudo dos distúrbios neurocognitivos perioperatórios, devido à combinação de fatores de risco específicos, incluindo resposta inflamatória sistêmica intensa, uso de circulação extracorpórea, microembolização cerebral e maior instabilidade hemodinâmica. Esses fatores contribuem para elevada incidência de delírium pós-operatório e declínio cognitivo nessa população, independentemente da técnica anestésica utilizada^{2,3}.

Ensaio clínico randomizado e estudos observacionais em cirurgia cardíaca não demonstram diferenças consistentes entre anestesia inalatória e TIVA quanto à incidência de delírium ou declínio cognitivo. Jiang et al. avaliaram pacientes submetidos a cirurgia valvar cardíaca e observaram incidência semelhante de delírium pós-operatório entre grupos anestesiados com agentes voláteis e aqueles submetidos à TIVA com propofol¹⁰. Esses achados sugerem que, nesse contexto, a magnitude do insulto inflamatório e metabólico associado ao procedimento cirúrgico supera o impacto isolado da escolha do agente anestésico.

Além disso, estudos que investigaram desfechos cognitivos tardios após cirurgia cardíaca não identificaram diferenças significativas entre técnicas anestésicas quando avaliados em períodos de médio e longo prazo. Esses resultados reforçam a noção de que, em cenários de agressão sistêmica intensa, como a cirurgia cardíaca, fatores como inflamação, microembolizações e alterações hemodinâmicas exercem papel predominante na gênese das alterações cognitivas pós-operatórias⁵.

3.6. Profundidade anestésica e fatores de confusão

Nos últimos anos, crescente atenção tem sido direcionada ao papel da profundidade anestésica como determinante independente dos desfechos neurocognitivos perioperatórios. Evidências acumuladas indicam que episódios de hipnose excessiva, frequentemente identificados por supressão eletroencefalográfica ou burst suppression, associam-se a maior risco de delírium pós-operatório e declínio cognitivo, independentemente do agente anestésico utilizado^{2,3}.

Estudos observacionais demonstram correlação entre maior tempo em supressão eletroencefalográfica e pior desempenho cognitivo no pós-operatório, sugerindo que a profundidade anestésica excessiva pode contribuir para disfunção neuronal transitória ou persistente¹⁰. Esses achados reforçam a importância da titulação individualizada da anestesia, idealmente guiada por monitorização eletroencefalográfica, como estratégia potencialmente mais eficaz para a prevenção das alterações cognitivas pós-operatórias do que a escolha isolada entre propofol e sevoflurano.

Além da profundidade anestésica, múltiplos fatores de confusão influenciam os desfechos neurocognitivos perioperatórios. Dor pós-operatória inadequadamente controlada, uso excessivo de opioides e benzodiazepínicos, episódios de hipotensão prolongada, hipoxemia e distúrbios do sono figuram entre os principais fatores associados ao aumento do risco de delírium e declínio cognitivo^{3,6}.

Esses fatores frequentemente coexistem e interagem de maneira complexa, tornando difícil a atribuição causal de alterações cognitivas pós-operatórias a um único elemento isolado. Assim, a prevenção eficaz dessas alterações requer abordagem multimodal e integrada, centrada na identificação e modificação de fatores de risco ao longo de todo o período perioperatório.

3.7. Implicações clínicas

A integração crítica das evidências experimentais, translacionais e clínicas apresentadas nesta revisão sugere que a técnica anestésica exerce influência limitada sobre os distúrbios neurocognitivos perioperatórios quando considerada isoladamente. O propofol parece oferecer vantagem na preservação cognitiva precoce em contextos específicos, particularmente em cirurgias

não cardíacas e em pacientes idosos, possivelmente em virtude de suas propriedades anti-inflamatórias e antioxidantes^{4,7}.

Entretanto, essa vantagem não se traduz de forma consistente em benefícios cognitivos sustentados a longo prazo. Em avaliações tardias, as diferenças entre propofol e sevoflurano tendem a desaparecer, sugerindo que o impacto da técnica anestésica sobre a cognição é transitório e superado por outros determinantes fisiopatológicos ao longo do tempo^{8,9}.

Em cenários de alta carga inflamatória sistêmica, como a cirurgia cardíaca, os dados disponíveis indicam que a escolha do agente anestésico tem impacto mínimo sobre os desfechos cognitivos, reforçando a importância de fatores como resposta inflamatória, microembolização cerebral e estabilidade hemodinâmica¹⁰.

Revisões narrativas contemporâneas reforçam que os distúrbios neurocognitivos perioperatórios resultam de um processo dinâmico e multifatorial, no qual a neuroinflamação atua como eixo central, mas não exclusivo. Evidências recentes destacam que ativação microglial, disfunção da barreira hematoencefálica, estresse oxidativo e alterações da conectividade funcional entre redes corticais e subcorticais ocorrem de forma interdependente, moduladas por fatores individuais e contextuais do paciente¹¹⁻¹³.

Esses dados sustentam a compreensão de que a anestesia geral deve ser interpretada como moduladora desses mecanismos fisiopatológicos, e não como fator etiológico isolado.

Estes achados têm implicações clínicas importantes. Eles sugerem que a prevenção das alterações cognitivas pós-operatórias deve priorizar estratégias globais de cuidado perioperatório, incluindo titulação individualizada da anestesia, monitorização da profundidade hipnótica, otimização hemodinâmica, controle rigoroso da dor e minimização do uso de fármacos potencialmente deletérios à cognição.

4. Conclusão

Os distúrbios neurocognitivos perioperatórios representam complicação frequente e clinicamente relevante, especialmente em pacientes idosos e vulneráveis. A evidência disponível sugere que o propofol pode estar associado a melhor preservação cognitiva no pós-operatório imediato em contextos específicos, particularmente em cirurgias não cardíacas. Contudo, não há evidência consistente de benefício sustentado a longo prazo em comparação ao sevoflurano.

Assim, a prevenção das alterações cognitivas pós-operatórias depende menos da escolha isolada entre propofol e sevoflurano e mais da qualidade global do manejo anestésico e perioperatório. A individualização do cuidado, a identificação precoce de fatores de risco e a adoção de estratégias multimodais permanecem os principais determinantes para a redução do impacto dessas alterações cognitivas no período pós-operatório.

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5.2 ARTIGO 2 REFERENTE AOS OBJETIVOS ESPECÍFICOS 2-5

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Cognitive Changes in Laparoscopic Cholecystectomy: Cognitive Assessments in Decision-Making Matters

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Article

Cognitive Changes in Laparoscopic Cholecystectomy: Cognitive Assessments in Decision-Making Matters

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Abstract

Background: Cognitive changes after minor surgery may affect patient safety, functional recovery, and readiness for hospital discharge, even after low-risk procedures with early discharge protocols. In this regard, patients require neuropsychological assessment at discharge, which may have important clinical implications for return to daily activities and postoperative decision-making. Our study investigated postoperative cognitive changes after minor surgery under general anesthesia using a neuropsychological assessment and a non-surgical group. **Methods:** Patients undergoing laparoscopic cholecystectomy received propofol or sevoflurane anesthesia. A non-surgical control group was included. Cognitive performance was assessed at baseline and discharge using the Computerized Visual Attention Test (CVAT), the controlled oral word association test (COWAT), and the symbol digit modalities test (SDMT). Relative change scores were calculated as ((baseline – postoperative performance)/baseline). Group differences were analyzed using two-tailed multivariate analysis of variance (MANOVA), followed by ANOVAs and Bonferroni-adjusted pairwise comparisons. **Results:** A total of 105 participants were included (37 non-surgical, 34 propofol, 34 sevoflurane). MANOVA showed a significant group effect (Pillai's trace = 0.332, $p < 0.001$, $\eta^2 = 0.196$). The ANOVAs revealed significant differences in sustained attention (CVAT), verbal fluency (COWAT) and executive function (SDMT). The propofol group showed evident decline in sustained attention compared to non-surgical. In verbal fluency, non-surgical improved at day after, whereas both surgical groups showed no improvement, indicating worse performance. In SDMT the sevoflurane group had worse performance. **Conclusions:** Minor surgery under general anesthesia may lead to transient impairments in attention and learning at discharge, supporting the need for postoperative cognitive monitoring and individualized discharge decisions.

Keywords: anesthesia; attention; neuroinflammation; postoperative cognitive dysfunction; propofol; sevoflurane; anesthesia; intravenous; anesthesia; inhalation



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1. Introduction

Although cognitive deficits have been observed during major surgeries since 1887, the underlying mechanisms remain incompletely understood [1]. The occurrence of specific cognitive deficits after minor surgical operations has been reported and can potentially interfere with patient safety and functional recovery during the immediate postoperative period [1–4]. Those alterations may affect attention subdomains, executive functioning,

psychomotor performance, and learning capacity, domains directly involved in activities required after hospital discharge [1–4]. The importance of this research is emphasized by the exponential increase in elective surgical procedures occurring every decade, projected to reach 5000 operations per 100,000 patients by 2030 [5]. In this context, laparoscopic cholecystectomy, due to its established safety profile and cost-effectiveness, is performed as ambulatory surgery in 90% of cases, typically with same-day discharge (SDD) [6]. All these discussions' trends highlight the need for cognitive assessment at hospital discharge [6].

Cognitive impairments can still happen due to the multifactorial pathophysiology [2]. Neuroinflammation and disruption of the blood–brain barrier have been proposed as central features [2,7]. It raises questions regarding their underlying mechanisms [2–4]. Anesthesiologists may reduce these risks with clinical personalized intraoperative anesthesia decisions, by maintaining physiological homeostasis and preventing intraoperative hypotension, hypoxemia, hypothermia, and excessive anesthetic depth [2,8]. Nevertheless, cognitive impairments can still happen due to the multifactorial pathophysiology [2]. Neuroinflammation and disruption of the blood–brain barrier have been proposed as central features [2,8].

Different anesthetic techniques have been investigated as potential modulators of postoperative cognitive outcomes. Propofol, an intravenous drug, has been shown to induce anti-inflammatory and antioxidant functions that may have neuroprotective effects in humans [9,10]; sevoflurane, an inhalant, has been linked with cognitive impairments, possibly because of its pro-inflammatory and neurotoxic activities [9,10]. These hypotheses have inspired several prospective randomized controlled trials and systematic reviews and meta-analyses comparing propofol and sevoflurane anesthesia. Although other studies indicate greater positive effects of propofol on cognitive impairments [11], their findings are inconclusive, owing to methodological limitations such as heterogeneity in cognitive testing and anesthesia protocols [12–14].

In this rationale, the present study was conducted to investigate postoperative cognitive changes after minor laparoscopic surgery under general anesthesia, using a non-surgical group to control for the learning effects associated with repeated neuropsychological testing. We compared preoperative baseline cognitive performance with performances on the discharge day as the primary outcome, and at 15 and 45 days as secondary outcomes. It was hypothesized that minor surgical procedures might be associated with cognitive changes and that propofol would protect against cognitive changes at hospital discharge.

The rationale of this study is explained in Figure 1.

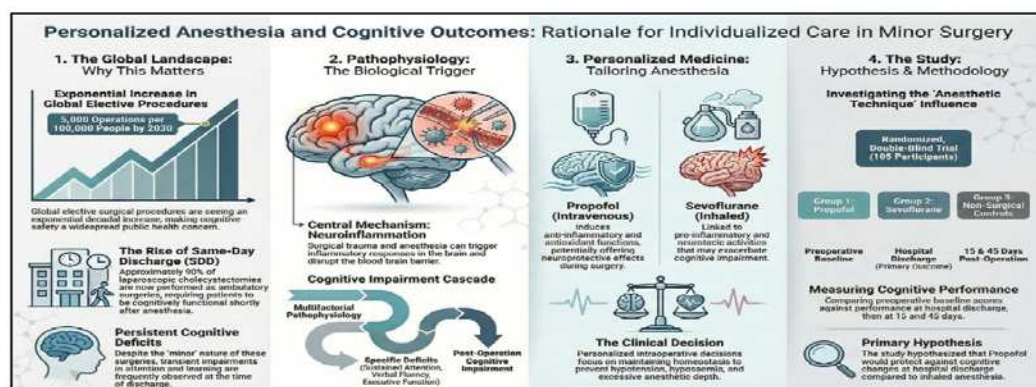


Figure 1. A schematic representation of rationale of this study. Created using NotebookLM® (Google, CA, USA, accessed on 9 March 2026).

2. Materials and Methods

2.1. Ethics

The study was prospectively registered with the Brazilian Clinical Trials Registry (ReBEC) (RBR-6xhp399; UTN code: U1111-1295-3640, approved on 8 August 2023) and was conducted at the Gaffrée and Guinle University Hospital of the Federal University of the State of Rio de Janeiro. The trial protocol was approved by the Research Ethics Committee of the same institution (CAAE: 54581221.0.0000.5258; Approval No.: 5.187.287 approved on 27 December 2021). The data were collected from September 2023 to September 2024. The present report is a partial analysis of a larger prospective research project.

2.2. Study Design

We conducted a single-center, randomized, controlled, double-blind, two-arm, parallel-group clinical trial in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki. The institutional review board approved the study, and written informed consent was obtained from all participants. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) 2025 guidelines for randomized controlled trials, and we used generative artificial intelligence (GenAI) to generate a graphic abstract and the figures included in this study; specifically, NotebookLM[®] (Google, based on large language models, accessed on 9 March 2026) was employed to create conceptual figures based on the authors' input and scientific content. All Gen AI images were critically reviewed, edited and validated by the authors to ensure accuracy and consistency with the scientific data presented.

Two well-established general anesthesia techniques, a propofol-based, total intravenous anesthesia (propofol group) and a sevoflurane-based, inhalation anesthesia (sevoflurane group), were compared to evaluate postoperative cognitive impairment. Surgical patients were randomly assigned to one of these two interventions. A non-randomized, non-surgical comparative group was included in the cohort to assess baseline cognitive performance as a control to allow differentiation between true postoperative changes and learning effects associated with repeated neuropsychological testing. This non-surgical group consisted of healthy volunteers (companions or relatives of the surgical patients) who met the same eligibility criteria as the surgical groups but were not exposed to anesthesia, surgery, perioperative pain, or hospitalization-related physiological stress factors. Although not randomized, the inclusion of this cohort provided an important methodological reference for interpreting postoperative cognitive trajectories over time and strengthened the identification of cognitive changes specifically associated with the perioperative period.

2.3. Participants

Eligible participants were adults older than 18 years with an ASA physical status of I or II who were scheduled for elective laparoscopic cholecystectomy under general anesthesia. Non-inclusion criteria included: ASA physical status III or IV; neurological or psychiatric disorders affecting cognition; chronic use of corticosteroids, antipsychotics, opioids, zolpidem, or tricyclic antidepressants; smoking or alcoholism; severe hepatic disease; renal insufficiency; inability to complete neuropsychological testing; postoperative delirium; perioperative protocol complications such as hemorrhage, hypoxemia, or hypotension; excessive anesthetic depth (defined as a significant number of intraoperative Bispectral Index [BIS] values ≤ 35); previous general anesthesia within the prior year; prior cardiac or neurological surgery; surgical duration exceeding 300 min; emergency surgery; or major intraoperative surgical complications.

2.4. Randomization, Group Allocation, and Blinding

Prior to participant enrolment, an independent researcher generated a computer-based randomization sequence using a 1:1 allocation ratio. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes, which were opened by the anesthesiologist responsible for administering general anesthesia on the day of surgery.

Blinding was achieved by ensuring that the investigators who conducted the pre-operative and postoperative neuropsychological assessments were different from those responsible for intraoperative anesthetic management. Both the patients and outcome assessors were blinded to group allocation. The anesthetic procedures were performed by four anesthesiologists working in collaboration with three separate surgical teams.

2.5. Cognitive Assessments

In our study, we used three tests: 1. the controlled oral word association test (COWAT) [15] 2. the symbol digit modalities test (SDMT) [16,17] and 3. the Computerized Visual Attention Test (CVAT) [18]. The assessments were conducted at four predefined time points: 1 day before surgery (baseline performance); on the day of hospital discharge (12–24 h postoperatively); 15 days after surgery (postoperative days 12–17) (D15); and 45 days after surgery (postoperative days 43–48) (D45). The same three neurocognitive tests were administered at each time point.

2.5.1. COWAT

The COWAT in the phonemic mode [15] measured verbal fluency and executive function. In the phonemic (FAS task), participants were instructed to produce as many words as possible beginning with the letters F, A, and S within 60 s for each letter, except for proper nouns, numbers, and morphological variations. The variable is the total number of correct answers. The COWAT is a validated tool and its sensitivity to frontal lobe dysfunction has been proved [15].

2.5.2. SDMT

Processing speed, fine motor coordination, and executive function were assessed using the SDMT [16,17]. Participants were instructed to match numbers to geometric symbols using a reference key within a 90 s time frame, with responses provided in written form. The variable is the total number of correct answers. To reduce learning effects and improve test–retest reliability, an alternative version of the SDMT was administered at baseline, on the day of discharge, and at D15, whereas the version administered at D45 was identical to that used at baseline [16,17].

2.5.3. CVAT

The CVAT was used to assess attention subdomains (Figure 2) [18]. In this study, we administered the 5 min version of CVAT with 120 stimuli, including 60 target and 60 non-target geometric shapes. In response to target stimuli, participants were instructed to press the spacebar as quickly as possible [18]. CVAT is an evidence-based instrument designed to measure multiple aspects of attention. To evaluate cognitive performance, we used four variables: omission errors (OE), commission errors (CE), corrected reaction time (RT) and corrected variability reaction time (VRT). Poor performance may manifest as OE, defined as number of failures to respond to target stimuli and deficits in focus attention [19–24]; CE, defined as number of incorrect responses to non-target stimuli, representing impaired inhibitory control and increased impulsivity [19–24]; RT, defined as time of reaction to target stimuli response, in milliseconds (ms), indicating slower visuomotor processing speed and reduced alertness [19–24]; and intra-individual VRT, defined as standard deviation of RT, is

the time of reaction to each target stimuli response in milliseconds, an increase in which is consistent with impaired sustained attention [19–24].



Figure 2. Provides a schematic overview of the CVAT task (target vs. non-target stimuli). Note: A schematic overview of the CVAT showing the target (star) and non-target (diamond). The test was conducted using a 13-inch laptop computer display (Windows® 10; maximum timing error: 30 ms) in a quiet room with only the participant and the examiner present. The subjects were seated approximately 50 cm from the screen and were required to have 20/30 visual acuity, with corrective lenses permitted [19]. The CVAT begins with written instructions displayed on the screen (A): “In this test, the computer alternately displays the indicated figures in the center of the screen. You must press the spacebar using your dominant hand as fast as you can whenever the star appears in the center of the screen. If the other figure appears, you should not press the spacebar.” The target (B) remains on the screen for 250 ms. The non-target (C) also remains on the screen for 250 ms. The test consisted of 120 trials (one figure presented at a time, either target or non-target). The interstimulus interval varied between 1, 2, and 4 s and was equally distributed throughout the test. The total test duration was 5 min. Variables: OEs, CEs, RT, and VRT (standard deviation of the RTs during the test). The CVAT is available for research and clinical use by licensed psychologists upon request, from Prof. Sergio L. Schmidt. Versions are available in English, Spanish, and Portuguese. CVAT: Continuous Visual Attention Test [18].

2.6. Anesthetic Management

General anesthesia was routinely administered in all surgical cases to avoid confounding related to inflammatory modulation. No anxiolytic or other preoperative medications were administered. All the patients received standard monitoring, including BIS monitoring. Anesthesia was induced with intravenous propofol ($1.0\text{--}2.0\text{ mg}\cdot\text{kg}^{-1}$) and a continuous infusion of remifentanyl ($0.10\text{--}0.5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Maintenance of anesthesia was achieved with continuous manual intravenous propofol ($50\text{--}100\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) in the propofol group or inhaled sevoflurane ($1\text{--}2\%$ minimum alveolar concentration) in the sevoflurane group. Anesthetic doses were clinically personalized in both groups to target a BIS value between 45 and 55. Tracheal intubation was facilitated with rocuronium ($0.6\text{--}1.2\text{ mg}\cdot\text{kg}^{-1}$), and supplemental doses ($10\text{--}20\%$ of the initial dose) were administered every 30 min as needed until the end of surgery, guided by train-of-four monitoring, and sugammadex administered, when necessary. Tracheal extubation was performed in the operating room, and all the patients were subsequently transferred to the post-anesthesia care unit. Hemodynamic and ventilatory parameters were closely regulated in accordance with a predefined intraoperative protocol to maintain intraoperative homeostasis.

Postoperative analgesia followed a clinical personalized multimodal regimen, including intravenous metamizole ($50\text{ mg}\cdot\text{kg}^{-1}$), surgical wound infiltration, and a transversus abdominis plane (TAP) block with bupivacaine ($1.0\text{--}2.0\text{ mg}\cdot\text{kg}^{-1}$). Intravenous tramadol ($50\text{--}100\text{ mg}$) was administered as rescue analgesia when the visual analog scale (VAS) score exceeded six. All the patients routinely received intravenous ondansetron (4 mg) at the end of surgery for prophylaxis of postoperative nausea and vomiting. Postoperative pain was assessed using the VAS and recording postoperative tramadol consumption. The incidence

of postoperative nausea and vomiting was monitored by recording the administration of ondansetron in the post-anesthesia care unit or on the day of hospital discharge.

Perioperative factors associated with postoperative cognitive impairment were actively and strictly controlled intraoperatively, including hypotension, hypoxemia, excessively deep anesthetic depth (BIS ≤ 35), hypothermia, hypercarbia and significant intraoperative bleeding. Patients who developed any of these protocol deviations were prospectively excluded from the study. The use of medications known to modulate inflammatory responses was prohibited throughout the study period, including dexmedetomidine, clonidine, dexamethasone and non-steroidal anti-inflammatory drugs, or drugs that interfere in cognitive outcomes, such as benzodiazepines and anticholinesterase agents. The rationale to this anesthetic protocol is explained in Figure 3.

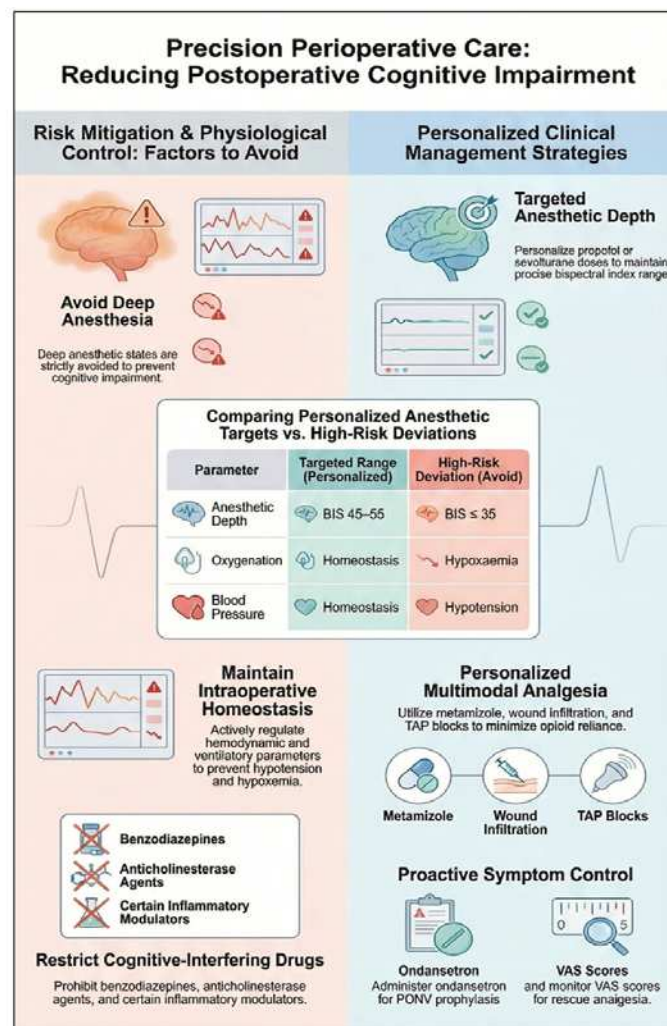


Figure 3. Schematic presentation of anesthetic protocol. Created using NotebookLM® (Google, accessed in 9 March 2026).

2.7. Demographic and Clinical Data

Demographic and clinical data were recorded, including age, sex, educational level, body surface area (BSA), ASA physical status, comorbidities, medication use, and history of prior surgery. Intraoperative hemodynamic parameters and total surgical or anesthesia durations were extracted from anesthesia records, and postoperative data were collected from the electronic medical record.

Postoperative delirium was screened using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), applied exclusively to the randomized surgical groups on the day of hospital discharge. The CAM-ICU is a validated instrument for detecting delirium, characterized by acute changes in mental status and altered levels of consciousness. A positive CAM-ICU result was considered an exclusion criterion [25].

2.8. Measurements to Assess Postoperative Changes

The primary outcome was to assess differences in cognitive performance between the three groups on the day of hospital discharge and baseline, using CVAT parameters (RT, VRT, CV, CE, and OE) and COWAT and SDMT scores. The secondary outcome was to evaluate differences in cognitive performance among the three groups at D15 and D45 after surgery using the same parameters.

To assess postoperative changes in cognitive performance, for the primary outcome, we first calculated a relative change score (ratio) for each variable using a formula that represents the proportion of baseline performance alterations on the first day after surgery.

Primary outcome: (baseline performance – postoperative day 1)/baseline performance.

For the secondary outcome, we used the same equation. This approach allowed the assessment of cognitive performance changes over time relative to baseline using the same directional framework as the primary outcome.

Secondary outcome: (baseline performance – Postoperative Day 15 or Day 45)/baseline performance.

Directional Alignment

The interpretation of ratio scores differed by variable type. For OE, CE, RT, and VRT, a negative ratio indicated a decline in performance (i.e., more errors, slower or more variable reaction times), while a positive ratio indicated improvement. For the COWAT and SDMT, the opposite pattern applied: a negative ratio indicated improvement (learning or practicing better performance on the second test), while a positive ratio indicated decline. This directional distinction was carefully considered when interpreting the results.

2.9. Sample Size

The sample size was calculated using the formula $N_p = [(Z_{\alpha/2} + Z_{\beta}) \cdot \sigma / D]^2$, where α = Type I error; $\alpha = 0.05$. β level was set at 0.20 and power (which = $1 - \beta$) was 0.80; σ = common standard deviation (based on previous test–retest reliability of CVAT study with 200 subjects) [18]; D = minimum difference accepted (D). The values of these differences were estimated assuming they would reach levels of clinical significance. Based on this consideration, the minimum sample size for the pairwise comparisons was 25 subjects per group. Given the approximately 10% loss to follow-up at each time point (D0, D15 and D45), we estimated that 34 participants per group would be required for the primary outcome. A formal MANOVA-based sample size calculation was not conducted because reliable a priori estimates of the multivariate covariance structure among the six cognitive outcome variables were not available. MANOVA was employed as an omnibus test to evaluate whether the intervention produced a significant overall effect across the set of cognitive outcomes while controlling the experiment-wise Type I error rate.

Only after establishing a significant multivariate effect were univariate ANOVAs examined to identify the specific cognitive domains contributing to the overall multivariate finding. Consequently, the univariate analyses should be viewed as protected follow-up tests rather than independent primary outcomes requiring separate sample size calculations.

2.10. Statistical Analysis

2.10.1. Baseline and Clinical Variables

As the non-surgical group was not included in the randomization process, differences in demographic, variables and baseline neurocognitive test raw scores among the three groups were compared using one-way univariate analyses of variance (ANOVAs). Intraoperative and postoperative variables were compared among the groups using independent-samples *t*-tests for continuous variables and chi-square tests for categorical variables, that included duration of surgery, duration of anesthesia, minimum BIS, minimum heart rate, minimum mean arterial pressure, SpO₂, and postoperative pain intensity (assessed by opioid consumption on the day of hospital discharge), and the occurrence of postoperative nausea and vomiting, as indicated by antiemetic administration, was evaluated. Pairwise comparison using ANOVA was performed between the non-surgical propofol and sevoflurane groups with VAS postoperative pain scores.

2.10.2. Multivariate Analysis

To determine whether declines were specific to the surgical groups, we performed a two-tailed multivariate analysis of variance (MANOVA) comparing the three groups (non-surgical, propofol, sevoflurane) on the ratio scores of all six variables. A significant multivariate effect ($p < 0.05$) would indicate an overall group difference in performance change and justify proceeding to univariate analyses. All assumptions for MANOVA were examined prior to analysis. Homogeneity of covariance matrices was assessed using Box's M test ($p > 0.001$), and no serious violations were detected.

2.10.3. Univariate Follow-Up

Following the MANOVA, we conducted univariate ANOVAs on each variable. Given our directional hypothesis that the surgical groups would show greater declines than the non-surgical group, we applied one-tailed tests for all variables. For OE, CE, RT, and VRT, the one-tailed hypothesis predicted that the surgical groups would have worse ratio scores than surgical, reflecting greater decline. For the COWAT and SDMT, the one-tailed hypothesis predicted that the surgical groups would have worse scores than the non-surgical groups. To control for Type I error due to multiple comparisons, we applied a Bonferroni correction. The use of one-tailed follow-up tests was prespecified and based on a directional hypothesis derived from the postoperative cognitive dysfunction literature. The primary research question was whether the patients undergoing surgery under general anesthesia would exhibit greater cognitive decline than non-surgical controls. No plausible theoretical or empirical rationale supported the opposite direction of effect, namely cognitive improvement attributable to surgery or anesthesia in the immediate postoperative period. Therefore, after establishing a significant overall multivariate effect through a two-tailed MANOVA, one-tailed univariate analyses were used to test the specific *a priori* hypothesis of postoperative cognitive deterioration.

2.10.4. Pairwise Comparisons

For variables with significant univariate effects, we performed pairwise comparisons with Bonferroni adjustment to identify specific group differences.

Statistical significance was defined as $p < 0.05$, consistent with the directional hypotheses established in the primary outcome analysis. All the analyses realized in the study were performed using SPSS version 31.0.0.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Participants

From September 2023 to September 2024, 110 patients were enrolled in the intervention groups and allocated to groups randomly (Figure 4). Of these, 68 patients completed the trial and had primary outcome data available at discharge, with 34 in the sevoflurane group and 34 in the propofol group. In the non-surgical group of the study, 55 participants were screened, of whom 37 were eligible and included in the primary outcome analysis. As for the secondary outcomes: 28 participants remained eligible at D15 and 25 at D45 in the non-surgical group due to loss to follow-up.

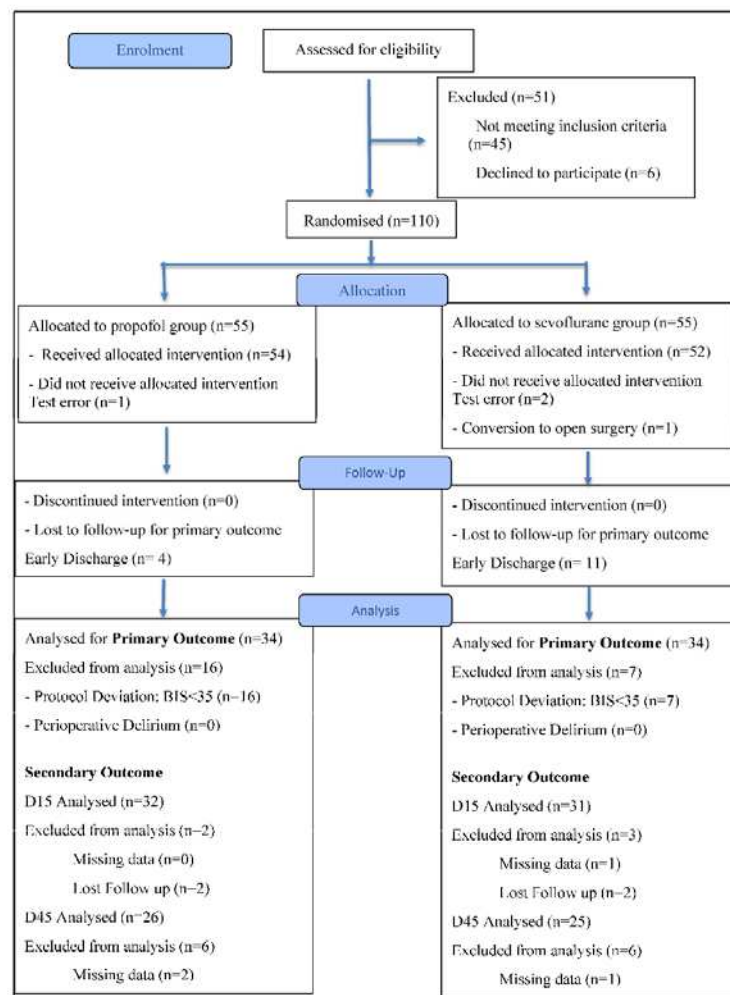


Figure 4. CONSORT 2025 Flowchart Diagram.

3.2. Demographic Data and Clinical Variables

The sample showed no significant differences in age, ASA, BSA, education and sex distribution were observed among the groups (Table 1). No significant difference in VAS pain or neuropsychological test scores was observed among the three groups at baseline (Table 1).

Table 1. A comparative analyses of demographic, clinical data and baseline neurophysiological performance among the propofol, sevoflurane and non-surgical groups.

Variable	Non-Surgical Group (n = 37)	Propofol Group (n = 34)	Sevoflurane Group (n = 34)	p Value
Demographic Data				
Age (years)	48.54 ± 16.8	53.27 ± 14	55.85 ± 14.02	0.145
Females (n, %)	25 (75.60%)	29 (85.28%)	28 (85.30%)	0.120
BSA (m ²)	1.88 ± 0.28	1.84 ± 0.21	1.90 ± 0.25	0.515
ASA Physical Status				
1 (n, %)	21 (56.75%)	16 (47.05%)	13 (38.23%)	0.302
2 (n, %)	16 (43.25%)	18 (52.94%)	21 (61.76%)	0.302
Education (years)	10.68 ± 3.12	9.74 ± 3.71	9.56 ± 3.31	0.299
VAS Discharge Day	0.667 ± 1.25	3.00 ± 2.83	3.28 ± 2.97	0.001
Baseline Neurophysiological Performance				
RT	459.24 ± 46.03	466.50 ± 62.14	471.32 ± 62.13	0.636
VRT	97.46 ± 25.06	97.82 ± 35.23	101.21 ± 44.77	0.911
OE	1.11 ± 1.58	2.09 ± 2.82	1.68 ± 2.46	0.168
CE	3.00 ± 2.73	2.62 ± 2.22	2.56 ± 2.11	0.727
COWAT	29.70 ± 10.66	27.97 ± 11.70	29.68 ± 12.93	0.781
SDMT	29.70 ± 12.01	28.68 ± 10.85	28.53 ± 14.96	0.910

Note: The data are presented as means ± SD for the continuous variables or numbers (n, %) for categorical variables. *p*-value was calculated with ANOVA. Bold values indicate statistical significance at the *p* < 0.05 level. Abbreviations: BSA: Body Surface Index (m²); y: years; RT, reaction time (milliseconds); VRT, variability reaction time (milliseconds); OE, omission error; CE, commission error; COWAT, controlled oral word association test; SDMT, symbol digit modalities test.

At hospital discharge, the mean VAS on discharge day in ANOVA showed significant difference among the groups (Table 1); in pairwise comparisons both the surgical groups had significantly higher pain scores than the non-surgical group (propofol vs. non-surgical: *p* < 0.001; sevoflurane vs. non-surgical: *p* < 0.001). No significant difference was observed between the propofol and sevoflurane groups (*p* = 0.505). Additionally, no patient screened positive for delirium on the CAM-ICU in any group.

As shown in Table 2, intraoperative hemodynamic parameters, length of hospital stay, total surgical and anesthesia durations, and postoperative outcomes were similar between the propofol and sevoflurane groups.

Table 2. Comparative analyses of the intraoperative and postoperative data between the propofol and sevoflurane groups. Note: The data are presented as means ± SD for the continuous variables or numbers (n, %) for categorical variables. *p*-value was calculated with *t*-test or χ^2 . Abbreviations: BIS, Bispectral Index; MAP, mean arterial pressure; HR, heart rate; PONV, postoperative nausea and vomiting.

Variable	Propofol Group (n = 34)	Sevoflurane Group (n = 34)	p Value
Intraoperative Data			
Duration of surgery (min)	100.0 ± 39.7	89.1 ± 33.5	0.226
Duration of anesthesia (min)	167.2 ± 44.1	158.5 ± 40.5	0.398

Table 2. Cont.

Variable	Propofol Group (<i>n</i> = 34)	Sevoflurane Group (<i>n</i> = 34)	<i>p</i> Value
BIS values (minimum)	41.0 ± 6.4	42.4 ± 4.7	0.295
MAP (mmHg)	108.7 ± 18.7	110.0 ± 19.0	0.775
HR (min)	61.9 ± 9.5	64.4 ± 10.5	0.336
SpO ₂ (%)	99.9 ± 0.2	100.0 ± 0.0	0.169
Cutaneous temperature; °C	36.0 ± 0.26	36.0 ± 0.27	0.616
EtCO ₂ ; mmHg	32.8 ± 5.79	32.5 ± 3.78	0.843
Length of hospital stay	1.32 ± 0.475	1.38 ± 0.493	0.618
Postoperative Data			
Postoperative opioids consumption	2 (5.8%)	3 (8.8%)	0.642
PONV	5 (14.70%)	3 (8.8%)	0.452

3.3. Primary Outcomes

3.3.1. Multivariate Analysis of Performance Changes

For the discharge day, the MANOVA revealed a significant multivariate effect of group; Pillai's Trace = 0.332, $F(12, 196) = 3.246$, $p < 0.001$, and partial $\eta^2 = 0.196$, indicating that the pattern of performance changes differed significantly across the three groups. This moderate-to-large effect size justified proceeding to univariate analyses.

3.3.2. Univariate Analysis for the Day of Hospital Discharge

Following the significant MANOVA, one-tailed univariate ANOVAs were conducted on each dependent variable. For OE, no significant group differences were observed ($p = 0.340$). For CE, univariate ANOVA approached reach significance ($p = 0.049$) and should be interpreted as a trend. RT showed no significant group differences ($p = 0.145$). VRT showed a significant effect, ($p = 0.025$). This indicates that anesthesia significantly affected the consistency of reaction time performance. COWAT demonstrated a significant effect of group ($p = 0.002$). The SDMT demonstrated a significant effect of group ($p = 0.005$).

3.3.3. Pairwise Comparisons

For VRT, the non-surgical group showed slight improvement, while both surgical groups demonstrated increased variability, indicating poorer sustained attention. Pairwise comparisons with Bonferroni adjustment revealed that the propofol group showed a more significant decline in VRT (increased variability) than the non-surgical group ($p = 0.034$). The sevoflurane group showed a non-significant trend to a worse performance than the non-surgical group ($p = 0.088$). No significant difference was observed between propofol and sevoflurane ($p = 0.500$).

For the COWAT (Figure 5), the non-surgical group showed a clear improvement, while the propofol and sevoflurane groups demonstrated no significant improvements. Pairwise comparisons with Bonferroni adjustment revealed that the propofol group showed a more significant decline (poor performance) than the non-surgical group ($p = 0.003$). The sevoflurane group also differs significantly from the non-surgical group, showing worse performance ($p = 0.021$). No significant difference was observed between the propofol and sevoflurane groups ($p = 0.500$).

COWAT comparison. Baseline vs. discharge day among groups.

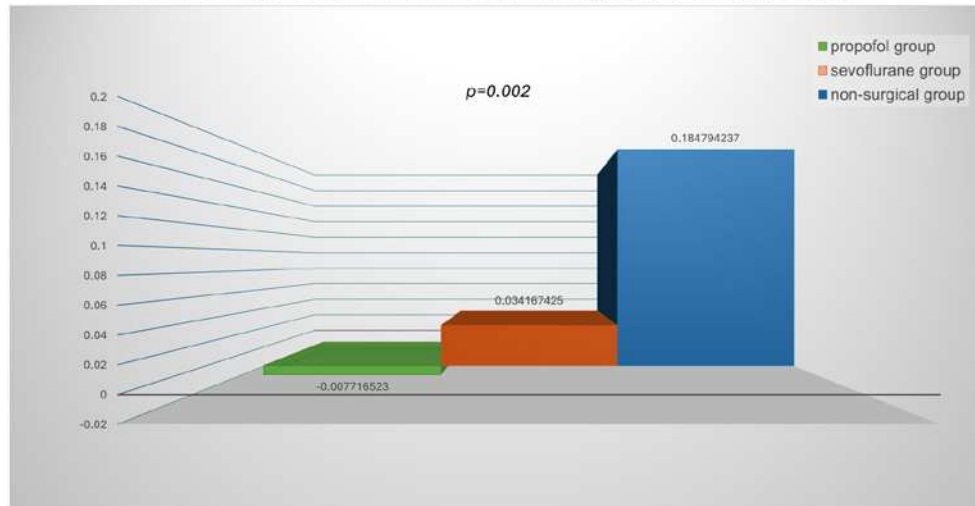


Figure 5. A COWAT comparison. Baseline vs. discharge day among the groups. Note: The data present the delta discharge COWAT values on discharge day using the formula $[(\text{baseline performance} - \text{discharge day performance}) / \text{baseline performance}]$, which showed a significant improvement among groups in ANOVA ($p = 0.002$), and a significant improvement in non-surgical groups when compared with the sevoflurane ($p = 0.021$) and propofol ($p = 0.003$) groups in pairwise comparisons.

For the SDMT, the non-surgical group showed a clear improvement and the propofol and sevoflurane groups presented no improvement. Pairwise comparisons with Bonferroni adjustment revealed that the non-surgical group showed significant improvement (better performance) than the sevoflurane group ($p = 0.004$). Non-surgical group showed a non-significant trend to an improved performance when compared to the propofol group ($p = 0.103$). No significant difference was observed between the propofol and sevoflurane groups ($p = 0.347$).

3.4. Secondary Outcomes

Multivariate Analysis of Performance Changes—D15 and D45

For D15, the MANOVA revealed a non-significant multivariate effect of group; Pillai's Trace = 0.067, $F(12, 168) = 0.484$, $p = 0.922$, and partial $\eta^2 = 0.168$. For D45, the MANOVA revealed a non-significant multivariate effect of group; Pillai's Trace = 0.093, $F(12, 140) = 0.571$, $p = 0.862$, and partial $\eta^2 = 0.140$. In both, the pattern of performance changes did not differ significantly across the three groups. These results did not justify proceeding to univariate analyses.

4. Discussion

At discharge day, as the primary outcome, sustained attention was affected in the surgical groups. In terms of a practice effect on the COWAT and SDMT, statistically significant differences in performance were observed between the non-surgical group and both surgical groups. The propofol and sevoflurane groups did not differ significantly on any neurocognitive test. In the secondary outcome, at D15 and D45, no significant difference was observed among the three groups.

An important finding of this study is the significant effect of anesthesia on VRT, a measure of sustained attention and response consistency. The propofol group showed significantly increased VRT, indicating poorer sustained attention, while the sevoflurane group showed a trend in the same direction. The sevoflurane group's intermediate position (worse than non-surgical but better than the propofol group, though not significantly different from either) suggests that inhalation anesthesia may confer relative protection of attentional function. This pattern is consistent in other studies, where propofol produced actual decline while sevoflurane produced only diminished learning [26,27]. Nevertheless, the direct comparison between propofol and sevoflurane did not reach statistical significance. The importance of these findings highlights the risk for attentional impairment in patients undergoing minor surgical procedures at the time of hospital discharge, as well as the possible need for neuropsychological assessment at this moment.

VRT is considered a pure measure of sustained attention, relatively free from the influence of motor speed or cognitive strategy [18–24]. Propofol and sevoflurane selectively impaired this function, suggesting that general anesthesia may have specific effects on attentional networks, potentially involving thalamocortical circuits or frontal attention systems (PFC) [28]. This mechanism involves increased release of noradrenaline and dopamine, leading to activation of lower-affinity adrenoceptors and a consequent reduction in neuronal firing within the PFC, which plays a central role in sustaining attention and integrating executive process [29]. These findings are consistent with previous evidence demonstrating transient modulatory effects of both propofol and sevoflurane on prefrontal cortical activity during general anesthesia, typically lasting a few hours and resolving thereafter [29]. Both agents reduce prefrontal metabolism and frontoparietal connectivity, which may result in slower information processing, which may affect increasing VRT [30]. Such transient disruption of prefrontal networks provides a plausible neurobiological explanation for the short-lived impairment in sustained attention observed at hospital discharge in the present study.

Persistent postoperative pain could affect the VRT, considering pain has long been correlated with poor attentional regulation [31–33]. In line with this interpretation, both surgical groups exhibited higher pain scores at discharge compared with the non-surgical group, with no difference between the propofol and sevoflurane groups, as expected [31]. The inducement of moderate acute pain may affect attention and is sometimes a discharge risk [32,33].

In contrast to VRT, RT did not differ between the preoperative and discharge measurements in any group. In this context, this dissociation between mean speed (RT) and consistency is clinically meaningful. Patients may maintain their average processing speed while becoming more inconsistent in their responses, reflecting lapses of attention rather than generalized slowing [21,23]. This finding corroborates prior research demonstrating increased VRT following sustained attention tasks, without significant changes in RT in patients with pain (fibromyalgia [31] and spinal [34]).

The clinically significant differences in COWAT performance between the non-surgical group and both surgical groups were driven by greater improvement in the non-surgical group, suggesting a practice effect restricted to this group [15]. COWAT tasks require not only lexical access and executive function but also sustained attention to maintain task focus throughout the testing period [15]. The absence of learning or practice effects in the surgical groups may be partially explained by impaired sustained attention, as reflected in increased VRT. Patients with poorer attention are less able to benefit from previous exposure to the task, resulting in diminished or absent practice effects.

Although the study explored whether propofol- and sevoflurane-based anesthesia would be associated with different postoperative cognitive profiles, our findings did not

demonstrate significant differences between these two groups. This result should be interpreted in the context of the conflicting evidence available in the literature [35–39].

The same happens with the SDMT, which demonstrated a better performance in the non-surgical groups in comparison to the surgical groups with statistical significance in the sevoflurane group, and a trend in the propofol group [16]. These findings are in line with earlier studies that documented early postoperative cognitive changes after propofol and sevoflurane anesthesia [26,27]. At postoperative days 15 and 45, a learning effect was noted in both the surgical and non-surgical groups, consistent with prior reports [37,38].

Although meta-analyses and systematic reviews have proposed a potential neuroprotective role of propofol in postoperative cognitive outcomes [4,12], the present study found no significant differences between propofol and sevoflurane regarding cognitive endpoints, contrary to the initial hypothesis of a protective effect of propofol. Additionally, recent well-designed studies [13] have also failed to demonstrate statistically significant differences between these two anesthetic approaches. Even though earlier controversial reports described greater impairment in the propofol group [14], our results indicate comparable cognitive performance between propofol and sevoflurane, with no statistically significant differences. However, this study was not formally powered for the three-group MANOVA framework or for detecting subtle differences between propofol and sevoflurane anesthesia.

Our study limitations comprehend the application of simplified neurocognitive assessment battery due to logistic limitations: in the COWAT we only used the phonetic form evaluation, which can be affected by education and cultural background [15]; in the CAVT we used a small version of five minutes, instead of fifteen minutes [18]; in the SDMT, we applied the test in smaller intervals than forty-five days, where a test–retest learning effect has been observed, which might hinder its capability to detect earlier cognitive changes [16,17].

A second limitation is that the sample size calculation was based on the anticipated between-group differences in cognitive performance derived from prior studies. A formal MANOVA-based sample size estimation was not performed because reliable estimates of the covariance structure among the multiple cognitive outcomes were unavailable at the design stage. However, the MANOVA yielded a partial η^2 of approximately 0.20, corresponding to a Cohen's f of approximately 0.49, which represents a moderate-to-large effect size. Given the final sample size of 105 participants distributed across three groups, the achieved statistical power for detecting the observed multivariate effect was high, indicating that the study was adequately powered for its primary multivariate analysis.

Another limitation of ours was a relatively small sample size due to losses to follow-up, particularly on postoperative days 15 and 45. Such attrition may have reduced the statistical power to detect subtle or late-stage cognitive changes, emphasizing the need for further studies with larger samples. In addition, post-randomization exclusion due to BIS < 35 may have affected group balance and introduced selection bias, particularly because exclusions were asymmetrically distributed between surgical groups. Finally, the validity of one-tailed follow-up tests should be interpreted cautiously given the multiple cognitive endpoints and the exploratory nature of the analyses.

Our strengths included the use of the CVAT; this method used the objective outcomes measured at the end of each of these days to limit examiner bias and the risk of learning effects, which has been a major strength of this study [40]. The CVAT provides an objective measurement of attentional status, has been shown to be relatively immune to the effect of educational level and is free from cultural bias, providing evidence for its application to different population groups [23,24]. The standardization of the anesthetic technique, meticulous control of perioperative factors, and the exclusion of inflammatory modulators reduce the bias of this study; the inclusion of a non-surgical comparison group was

especially useful as it allowed us to identify a learning effect that was not present in the surgical patients.

The present study represents one component of a broader approved research protocol. Future investigations will analyze the remaining variables included in the original protocol, such as biomarker analyses, including S100 β assessment, as well as additional neuropsychological evaluations.

5. Conclusions

Minor surgery under general anesthesia may lead to transient impairments in attention and learning at the time of hospital discharge. No significant differences were observed between the propofol and sevoflurane groups, although, exploratory analysis suggested postoperative cognitive changes in the surgical patients compared with the non-surgical group. These findings support the potential value of postoperative cognitive monitoring and individualized discharge decisions.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

CVAT	Computerized Visual Attention Test
COWAT	Controlled Oral Word Association Test
SDMT	Symbol Digit Modalities Test
SDD	Same-Day Discharge
ReBEC	Brazilian Clinical Trials Registry

RBR-6xhp399	Trial registration ID (ReBEC)
UTN	code (not expanded in the text)
U1111-1295-3640	UTN trial code
CAAE	Ethics committee ID code (not expanded in the text)
No.	Number (as in "Approval No.")
CONSORT	Consolidated Standards of Reporting Trials
ASA	American Society of Anesthesia Physical Status
BIS	Bispectral Index
D15	Day 15 (postoperative)
D45	Day 45 (postoperative)
FAS	Phonemic task using letters F, A, S
OE	Omission Errors
CE	Commission Errors
RT	Reaction Time
VRT	(Intra-individual) Variability in Reaction Time
TAP	Transversus Abdominis Plane (block)
VAS	Visual Analog Scale
BSA	Body Surface Area
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
Np	Used in sample size formula (not defined in the text)
$Z_{\alpha/2}$	Z value for $\alpha/2$
Z_{β}	Z value for beta
α	Type I Error (<i>alpha</i>)
β	Beta level
σ	Common standard deviation
D	Minimum accepted difference
SpO ₂	Peripheral Oxygen Saturation
MANOVA	Multivariate Analysis of Variance
ANOVA/ANOVAs	Analysis of Variance
SPSS	Statistical Package for the Social Sciences
Inc.	Incorporated
IL	Illinois
USA	United States of America
df	Degrees of Freedom
p	p -value
F	F statistic
η^2/η^2	Eta Squared (effect size)
M	Mean
SE	Standard Error
ms	milliseconds

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7 DISCUSSÃO

A presente tese deriva de um protocolo prospectivo previamente registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC - RBR-6xhp399; UTN U1111-1295-3640), concebido para investigar diferentes aspectos da recuperação neurocognitiva após cirurgia e anestesia geral. O projeto original foi desenvolvido a partir da hipótese de que diferentes técnicas anestésicas poderiam exercer influência distinta sobre os desfechos cognitivos pós-operatórios, especialmente em razão das diferenças biológicas descritas entre propofol e sevoflurano em estudos experimentais. Entretanto, os resultados obtidos ao longo da investigação conduziram a uma reflexão mais ampla sobre a natureza da recuperação cognitiva e sua relação com a recuperação clínica tradicionalmente utilizada para definição da alta hospitalar.

A revisão narrativa realizada durante a fase inicial do projeto demonstrou que, embora existam evidências experimentais sugerindo propriedades anti-inflamatórias e potencial neuroprotetor do propofol, assim como associações entre anestésicos inalatórios e mecanismos relacionados à neuroinflamação, os estudos clínicos permanecem inconclusivos quanto à superioridade de uma técnica anestésica sobre outra (Amare; Mc Evoy; Smith, 2019; Chen *et al.*, 2022; Kletecka *et al.*, 2019; Negrini *et al.*, 2022). Essa discrepância entre achados laboratoriais e resultados clínicos sugere que as alterações cognitivas observadas no período pós-operatório provavelmente resultam de uma interação multifatorial envolvendo cirurgia, anestesia, resposta inflamatória, dor, privação de sono, estresse fisiológico e características individuais do paciente (Luo; Qiu; Wu, 2025; Safavynia; Goldstein, 2019).

O ensaio clínico prospectivo desenvolvido a partir desse racional confirmou essa hipótese. Não foram observadas diferenças significativas entre propofol e sevoflurano em nenhum dos momentos avaliados, tanto no pós-operatório imediato quanto durante o seguimento realizado após 15 e 45 dias (Apêndice F). Esses resultados encontram-se em consonância com revisões sistemáticas e metanálises recentes, reforçando a interpretação de que a escolha do agente anestésico isoladamente pode não representar o principal determinante da recuperação cognitiva após procedimentos cirúrgicos de pequeno porte (Chen *et al.*, 2022; Kletecka *et al.*, 2019; Negrini *et al.*, 2022).

Entretanto, a ausência de diferenças entre as técnicas anestésicas não representou um resultado negativo. Ao contrário, permitiu direcionar a análise para um achado potencialmente mais relevante do ponto de vista clínico: a identificação de alterações cognitivas transitórias no momento da alta hospitalar. Quando comparados a indivíduos não submetidos à cirurgia, os pacientes operados apresentaram alterações em parâmetros relacionados à atenção sustentada (Figura 3) e à aprendizagem verbal (Figura 4), sugerindo que a recuperação neurocognitiva pode permanecer incompleta mesmo após a resolução dos critérios clínicos tradicionalmente utilizados para definição da alta.

Figura 3: O declínio da atenção sustentada (CVAT)

O Declínio da Atenção Sustentada (CVAT)

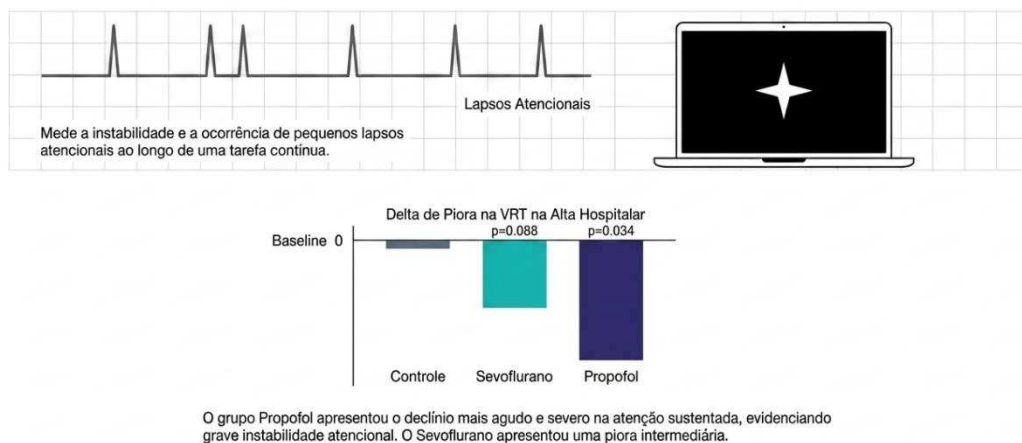
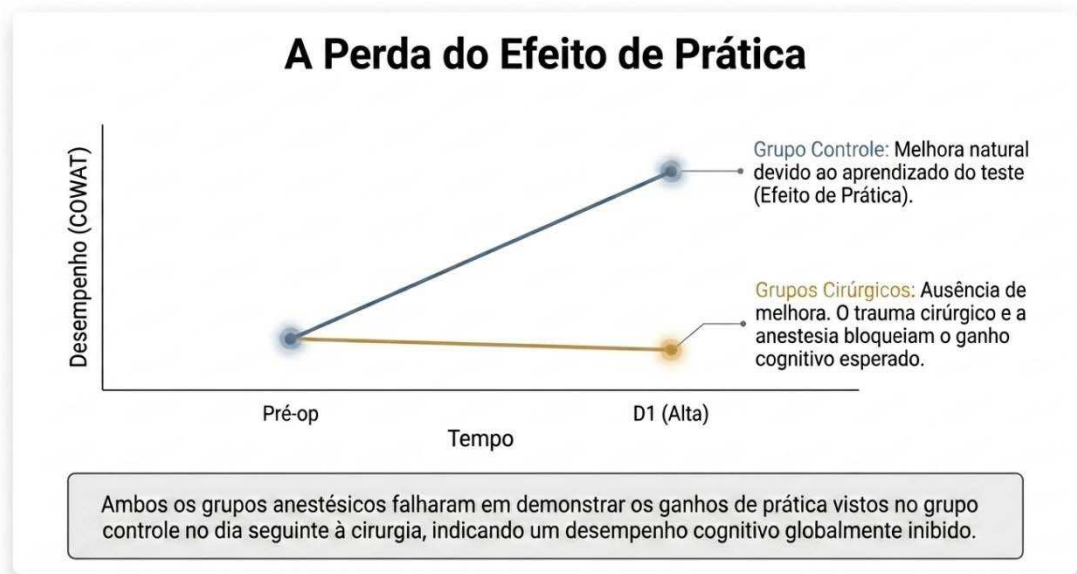


Figura 4: A perda do efeito de prática



Esse achado assume particular importância no contexto atual da medicina perioperatória. O desenvolvimento de programas de recuperação acelerada e a crescente realização de procedimentos ambulatoriais têm reduzido progressivamente o tempo de permanência hospitalar (Rohi; Olofsson; Jakobsson, 2022). Como consequência, pacientes recebem alta em períodos cada vez mais precoces e passam rapidamente a assumir responsabilidades relacionadas ao autocuidado, à administração de medicamentos, à compreensão de orientações médicas e ao reconhecimento de possíveis complicações pós-operatórias (Rohi; Olofsson; Jakobsson, 2022). Todas essas atividades dependem de funções cognitivas preservadas, especialmente atenção, memória operacional e capacidade de tomada de decisão (Filho *et al.*, 2022).

Entre os diferentes domínios avaliados, a atenção sustentada emergiu como o componente mais consistentemente associado às alterações observadas. A atenção sustentada corresponde à capacidade de manter desempenho estável ao longo do tempo durante tarefas contínuas e constitui um elemento fundamental para o funcionamento de diversos processos cognitivos superiores. Sua relevância transcende o desempenho em testes neuropsicológicos, influenciando diretamente a capacidade do indivíduo de processar informações, manter vigilância, executar

tarefas complexas e responder adequadamente às demandas do ambiente (Filho *et al.*, 2022; Schmidt *et al.*, 2019).

A escolha do CVAT mostrou-se particularmente adequada para essa investigação. Diferentemente de muitos instrumentos tradicionais, o CVAT permite a avaliação independente de diferentes subdomínios da atenção, possibilitando identificar quais mecanismos específicos estão envolvidos nas alterações observadas (Schmidt *et al.*, 2019). Nesse contexto, a VRT destacou-se como uma medida especialmente sensível. O aumento dessa variável sugere instabilidade do desempenho cognitivo e ocorrência de lapsos atencionais transitórios, refletindo comprometimento da atenção sustentada mesmo quando o desempenho médio permanece aparentemente preservado.

A importância desse achado é reforçada pelo fato de que não foram identificados casos de delirium pós-operatório entre os participantes avaliados (Miranda *et al.*, 2023). Dessa forma, as alterações observadas não podem ser atribuídas a uma síndrome neuropsiquiátrica aguda reconhecida clinicamente, mas sim a déficits cognitivos sutis detectáveis apenas por instrumentos específicos de avaliação neuropsicológica. Esse resultado reforça a necessidade de compreender as alterações cognitivas perioperatórias como um espectro amplo de manifestações, que inclui desde quadros evidentes, como o delirium, até alterações discretas e potencialmente transitórias que podem passar despercebidas na prática clínica habitual (Safavynia; Goldstein, 2019).

Outro aspecto relevante refere-se à evolução temporal dos achados. As diferenças observadas no momento da alta hospitalar não persistiram nas avaliações subsequentes, sugerindo que as alterações identificadas possuem caráter transitório e tendem à recuperação espontânea ao longo das semanas seguintes ao procedimento (Figura 5). Essa observação é clinicamente tranquilizadora, mas não reduz sua importância. Pelo contrário, reforça a necessidade de compreender o período de alta como uma fase particularmente vulnerável da recuperação pós-operatória, durante a qual déficits temporários podem coexistir com aparente normalização clínica (Rohi; Olofsson; Jakobsson, 2022).

Figura 5: O caráter transitório da lesão

O Caráter Transitório da Lesão



A lesão induzida por cirurgias de pequeno porte **não é permanente**. Contudo, **o risco no momento exato da alta hospitalar (D1)** é agudo, real e, até agora, invisível aos protocolos padrão.

NotebookLM

Algumas limitações devem ser consideradas. O estudo foi realizado em centro único, incluindo predominantemente pacientes com baixo risco cirúrgico submetidos a um único tipo de procedimento. Além disso, o grupo não cirúrgico não foi randomizado, devendo as comparações entre grupos ser interpretadas com cautela. Por outro lado, a utilização de protocolo anestésico rigorosamente padronizado, a avaliação neuropsicológica seriada, o controle dos efeitos de aprendizagem e o registro prévio do protocolo constituem importantes pontos fortes metodológicos.

Entre os principais pontos fortes desta investigação destacam-se o delineamento prospectivo, randomizado e duplo-cego, aliado à padronização rigorosa do manejo anestésico e dos parâmetros fisiológicos intraoperatórios, conferindo elevada validade interna ao estudo. A utilização de uma bateria neuropsicológica composta por instrumentos validados e complementares (CVAT, COWAT e SDMT) possibilitou uma avaliação abrangente de diferentes domínios cognitivos, enquanto o emprego do CVAT permitiu analisar separadamente os subdomínios da atenção, identificando a atenção sustentada, representada pela variabilidade do tempo de reação, como o componente mais sensível às alterações pós-operatórias. A inclusão de um grupo não cirúrgico possibilitou controlar os efeitos de aprendizagem decorrentes da repetição dos testes, fortalecendo a interpretação dos resultados, e o acompanhamento longitudinal até 45 dias permitiu demonstrar o caráter transitório das alterações observadas. Adicionalmente, a

avaliação sistemática do delirium por meio do CAM-ICU excluiu essa condição como fator de confusão, enquanto o registro prévio do protocolo no Registro Brasileiro de Ensaios Clínicos (ReBEC) assegurou transparência metodológica e reforçou a robustez científica do estudo. Finalmente, esta é, ao nosso conhecimento, a primeira investigação a utilizar o CVAT para avaliar sistematicamente a recuperação cognitiva após cirurgias de pequeno porte, propondo a atenção sustentada como um potencial biomarcador comportamental da recuperação cognitiva pós-operatória.

Finalmente, os resultados desta tese devem ser interpretados como parte de um programa de pesquisa mais amplo. O protocolo original contemplava diferentes desfechos clínicos, neuropsicológicos e laboratoriais, cujas análises futuras poderão contribuir para uma compreensão mais abrangente dos mecanismos envolvidos na recuperação neurocognitiva pós-operatória. Nesse contexto, os achados aqui apresentados representam um passo importante na construção de uma nova perspectiva sobre a recuperação perioperatória, incorporando a dimensão cognitiva como componente fundamental da avaliação da qualidade da recuperação.

8 CONCLUSÃO

A presente tese demonstrou que pacientes submetidos a cirurgias de pequeno porte sob anestesia geral podem apresentar alterações cognitivas transitórias no período pós-operatório imediato, mesmo quando considerados clinicamente aptos para alta hospitalar, reforçando que a recuperação cognitiva constitui uma dimensão complementar da recuperação clínica. A revisão da literatura e os resultados do ensaio clínico evidenciaram que, embora propofol e sevoflurano apresentem diferenças farmacológicas e mecanismos experimentais distintos, não houve diferenças significativas entre as técnicas anestésicas quanto aos desfechos neuropsicológicos avaliados. A avaliação por meio do CVAT, do COWAT e do SDMT permitiu identificar alterações cognitivas sutis no período pós-operatório imediato, destacando a atenção sustentada, particularmente a variabilidade do tempo de reação, como o domínio cognitivo mais sensível. Essas alterações mostraram-se transitórias, com recuperação do desempenho cognitivo aos 15 e 45 dias de pós-operatório. Em conjunto, os achados ampliam a compreensão sobre a recuperação cognitiva após cirurgias de pequeno porte e sustentam a hipótese de que a atenção sustentada representa um potencial biomarcador comportamental da recuperação cognitiva pós-operatória, podendo futuramente contribuir para estratégias mais seguras e individualizadas de avaliação da prontidão para alta hospitalar.

9 PERSPECTIVAS FUTURAS

Os resultados desta tese apontam para a necessidade de aprofundar a compreensão dos mecanismos envolvidos na recuperação cognitiva após cirurgia e anestesia. Uma das principais etapas futuras deste programa de pesquisa será a análise dos biomarcadores biológicos previstos no protocolo original registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC RBR-6xhp399; UTN U1111-1295-3640), do qual esta tese representa uma análise parcial. A dosagem seriada de marcadores inflamatórios, como proteína C reativa (PCR), interleucina-6 (IL-6), interleucina-1 β (IL-1 β) e fator de necrose tumoral alfa (TNF- α), permitirá investigar a associação entre a resposta inflamatória perioperatória e as alterações cognitivas observadas, contribuindo para o esclarecimento dos mecanismos biológicos relacionados à vulnerabilidade da atenção sustentada após cirurgia e anestesia.

Além disso, estudos futuros deverão avaliar a reprodutibilidade desses achados em diferentes populações cirúrgicas, incluindo pacientes idosos, frágeis e submetidos a procedimentos de maior complexidade, bem como investigar a integração entre avaliação neuropsicológica e biomarcadores biológicos. A validação da atenção sustentada como biomarcador da recuperação cognitiva poderá contribuir para a incorporação de instrumentos objetivos de monitorização cognitiva aos protocolos perioperatórios, permitindo decisões de alta mais seguras e individualizadas. Dessa forma, a continuidade das análises previstas no protocolo original poderá ampliar o conhecimento sobre as alterações cognitivas pós-operatórias e favorecer o desenvolvimento de estratégias voltadas para uma recuperação perioperatória mais completa e centrada no paciente.

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APÊNDICE A - Artigo publicado “Assessment of Attentional Functioning in Health Professionals of a Brazilian Tertiary Referral Hospital for COVID-19”

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Research Article

Assessment of Attentional Functioning in Health Professionals of a Brazilian Tertiary Referral Hospital for COVID-19

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This study is aimed at assessing differences in basic attentional functioning between substantial and minimal work-related exposure to COVID-19 patients in professionals working in a tertiary referral hospital in Rio de Janeiro, Brazil. Therefore, hospital employees performed a Continuous Visual Attention Test. This test consisted of a 90-second Go/No-Go task with 72 (80%) targets and 18 (20%) nontargets. For each participant, reaction time and intraindividual variability of reaction times of all correct target responses, as well as the number of omission and commission errors, were evaluated. Participants were divided into 2 groups based on their exposure to COVID-19 patients (substantial versus minimal exposure). The substantial exposure group consisted of participants with 24 hours/week or more direct contact with COVID-19 patients. This cut-off was based on the clear division between professionals working and not working with COVID-19 patients and considered that 12-hour and 24-hour daily shifts are common for hospital employees in Brazil. A MANCOVA was performed to examine between-group differences, using age, sleep quality, sex, education level, previous COVID-19 infection, and profession as covariates. Of 124 participants, 80 had substantial exposure and 44 had minimal exposure to COVID-19. The overall MANCOVA reached statistical significance ($P = 0.048$). Post hoc ANCOVA analysis showed that the substantial exposure group had a statistically significantly higher intraindividual variability of reaction time of all correct target responses ($P = 0.017$, Cohen's $d = -0.55$). This result remained after removing those with a previous COVID-19 infection ($P = 0.010$, Cohen's $d = -0.64$) and after matching groups for sample size ($P = 0.004$, Cohen's $d = -0.81$). No other variables reached statistical significance. Concluding, hospital professionals with a substantial level of exposure to patients with COVID-19 show a significant attention decrement and, thus, may be at a higher risk of accidental SARS-CoV-2 infection.

1. Introduction

Since the outbreak of the COVID-19 pandemic, health care professionals are at a high risk to be infected by the SARS-CoV-2 virus and are prone to develop psychological problems. Indeed, a large study in more than 1,200 health care professionals from 34 different hospitals in China has shown that symptoms of depression, anxiety, stress, and insomnia were particularly prevalent [1]. Thus, it is important to identify the psychological burden of professionals working in tertiary referral hospitals for COVID-19, including not only physicians and nurses, but also laboratory technicians, psychologists, physiotherapists, security, and administrative personnel.

There could be numerous reasons why health care professionals may experience adverse psychological effects during this pandemic, including little or no training to assist patients with anxiety, panic, and other emotional problems, a lack of sufficient protective equipment, increasing work load and concomitant fatigue, and feelings of inadequacy in treating critically ill patients [2, 3]. Previous studies not related to COVID-19 have indeed shown that long working hours under stressful conditions increase the risks of mental health complications [4]. Thus, another factor that could impact psychological well-being of health care personnel is the total exposure time, that is, how many hours a week they directly work with COVID-19 patients. The amount of time workers spend doing activities with COVID-19 patients may increase risk of infection and psychological burden. However, the effect of exposure time to COVID-19 on psychological health is not known.

Besides psychological distress and burden, health care professionals may also be faced with (transient) cognitive effects, which may be related to the aforementioned psychological symptoms. Whether these possible alterations improve with improving psychological well-being, either naturally or via therapy, is unknown. However, experiencing cognitive problems can directly affect work performance, worsen feelings of distress, depression, and anxiety, and increase worrying [5, 6], which could ultimately lead to a vicious cycle and burnout.

Attention is the ability to choose and concentrate on relevant stimuli and is considered a core human cognitive function [7, 8]. Thus, a decrease in attentional performance could lead to a higher risk of accidental SARS-CoV-2 infection, as workers might be more prone to make mistakes. Despite the importance of attention performance for cognitive functioning and work safety, we have not found studies on attention assessment in health care professionals working with COVID-19 patients.

Basic attention can be reliably measured by simple reaction time or Go/No-Go tasks, which have commonly the advantage of relying less on intelligence and education level than more complicated neuropsychological tests [7]. One such Go/No-Go test, the Continuous Visual Attention Test (CVAT), has been shown to be capable to detect attentional alterations in various conditions, including ADHD [9], chronic pain [10], and in people with obstructive sleep apnea [11]. Besides reaction time and errors, this test produces

intraindividual variability of reaction time. This measure can be considered as the fluctuation in reaction time during test performance and as such a lower variability indicates a more stable performance in terms of reaction time. Moreover, variability is considered a prime measure and has been linked to various attentional, including sustained attention [11], cognitive [12], and psychological processes [13].

Considering the importance of attentional functioning for work and mental well-being, we set out to measure attention in health care professionals with substantial and minimal exposure time to COVID-19 working in a COVID-19 tertiary referral hospital in Rio de Janeiro, Brazil. In this study, we determined the effect of exposure time to COVID-19 patients on attentional functioning, hypothesizing that the group with substantial exposure time would have worse functioning as compared to the group with minimal exposure time.

2. Materials and Methods

2.1. Participants. This study was approved by the Medical Ethics Committee of the University Hospital Gaffrée and Guinle and by the federal Medical Ethics Committee (CAAE: 30547720.3.0000.0008). The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. Inclusion criteria for this study were an age between 20 and 60 years and being a hospital employee. Exclusion criteria for this study included conditions that may interfere with attentional performance, such as any previous or current neurological disorder or diabetes and the use of benzodiazepines, antidepressants, all hypnotic sedatives, all antipsychotics, antiallergics that cross the blood brain barrier, glucocorticoids, or all muscle relaxants. Additionally, participants were excluded when they had less than 50% correct responses on the CVAT task, which indicates a performance below chance level, or when they performed the test at the end of their work day, to control for potential effects of fatigue on performance.

2.2. Exposure to COVID-19 Patients. Every participant was asked about his/her recent exposure to COVID-19 patients in the past week. Two groups were created one with substantial and one with minimal exposure to COVID-19 patients, with a cut-off of 24 hours of exposure. This cut-off was chosen as in Brazil 12-hour and 24-hour daily shifts are common for medical employees, psychologists, physiotherapists, and laboratory professionals working in hospitals, and contractual working hours consisted of 24 or 40 hours a week. Furthermore, in this tertiary hospital, there was a clear division between professionals working and not working with COVID-19 patients. Thus, participants had either no to minimal exposure or substantial exposure to COVID-19 as can also be found in Table 1.

2.3. Attentional Functioning. For this study, a 90-second computerized Go/No-Go test was used (Figure 1). The target stimulus consisted of a star presented in the middle of the screen, whereas the nontarget stimulus was a diamond. The CVAT consisted of one block of 90 trials, each trial being

TABLE 1: Group characteristics of all included participants.

	Minimal exposure to COVID-19	Substantial exposure to COVID-19	P value
N	44	80	-
Age (years)	39.61 ± 10.68	42.71 ± 10.02	0.110
Sex (male/female; % male)	15/29 (34.1)	28/52 (35.0)	0.999
Education level			0.014
Elementary level (%)	0 (0.0)	1 (1.3)	
High school level (%)	0 (0.0)	10 (12.5)	
Bachelor or higher (%)	44 (100.0)	69 (86.3)	
Exposure time to COVID-19 (%)			-
5 hours or less	28 (63.6)	-	
6 to 11 hours	10 (22.7)	-	
12 to 23 hours	6 (13.6)	-	
24–35 hours	-	16 (20.0)	
36–47 hours	-	48 (60.0)	
48 or more hours	-	16 (20.0)	
Self-reported poor sleep quality (last 2 weeks)			0.639
Never	7 (15.9)	19 (23.8)	
Less than a week	14 (31.8)	26 (32.5)	
More than a week	11 (25.0)	20 (25.0)	
Almost all days	12 (27.3)	15 (18.8)	
Previous COVID-19 infection (%)	4 (9.1)	18 (22.5)	0.085
Profession*			0.260
Medical/paramedical (%)	28 (63.6)	42 (52.5)	
Other (%)	16 (36.6)	38 (47.5)	
Attentional performance			Cohen's δ
Reaction time (ms)	371.33 ± 35.44	389.63 ± 49.08	-0.41
Variability of reaction times (ms)	64.62 ± 16.19	79.53 ± 31.98	-0.55
Coefficient of variability	0.17 ± 0.04	0.20 ± 0.06	-0.56
Commission errors (min-max)	2 (0–10)	3 (0–10)	-0.29
Omission errors (min-max)	0 (0–21)	1 (0–31)	-0.27

Data are presented as mean with standard deviation, absolute numbers with minimum and maximum, or as absolute numbers with percentages between parentheses. *Medical and paramedical professions included medical doctors and medical residents, nurses, physiotherapists, and psychologists. Other professions included nutritionists, pharmacists, engineers, and administrative, security, and laboratory employees.



FIGURE 1: Schematic overview of the set-up of the laptop and of the target (star) and nontarget (diamond).

presented for 250 ms, with an interstimulus interval of 750 milliseconds and a stimulus onset asynchrony of 1 second. Of the 90 trials, 72 (80%) were targets (stars), and 18 (20%) were nontargets (diamonds).

Subjects were seated in front of the computer in such a way as to allow the hands to be comfortably placed over the

keyboard, and that the distance to the center of the monitor was approximately 50 cm. Instructions were shown on the screen and then reinforced by the examiner. A practice session, in which no errors could be made, was presented before testing commenced. In the case of errors, the practice session was automatically repeated.

For each participant, the mean reaction time of correct responses to the target was calculated. Additionally, as reaction times will vary throughout the test, intraindividual variability of all reaction times of the correct responses to the target was also determined. Here, each individual's variability was calculated by using the standard deviation of the individual distribution of all reaction times of the correct responses to the target. Intraindividual variability of reaction times may depend on reaction time itself. This indicates that, in case of a difference in reaction time, possible alterations in intraindividual variability might be influenced by reaction time itself [14, 15]. To circumvent this potential bias, we calculated the coefficient of intraindividual variability, which is calculated as the intraindividual variability divided by reaction time. Lastly, omission errors (no response to a target) and commission errors (response to a nontarget) were calculated.

Fast responses, those faster than 150 ms, are most likely physiologically implausible. Therefore, those fast responses were removed, and for those participants, the mean reaction time, intraindividual variability of all reaction times, and the coefficient of variability were recalculated.

2.4. Statistical Analyses. Demographic variables were analyzed using an independent sample *t*-test for normally distributed variables, a Kruskal-Wallis test for nonnormally distributed variables, or a χ^2 test for categorical variables. Normality of variables was confirmed by assessing the histograms, boxplots, and QQ plots. Effect sizes were calculated as Cohen's δ , where a $\delta = 0.20$ is considered a small effect, a $\delta = 0.50$ a medium effect, and $\delta = 0.80$ or higher a large effect [16].

First, a MANCOVA was performed including reaction time, variability of reaction time, omission and commission errors as dependent variables, and exposure to COVID-19 (minimal or substantial) as independent variable. This analysis was corrected for age, sex, sleep quality, education level, previous COVID-19 infection, and profession. Sleep quality was defined by asking the participant to rate the quality of their sleep in the past 2 weeks. Box's M test was used to assess the homogeneity of the covariance matrices. In case of a significant overall MANCOVA, the post hoc ANCOVA of each of the dependent variables was checked for statistical significance. A significant MANCOVA indicates that at least one dependent variable is different between the groups, thus allowing for further post hoc testing. A MANCOVA/ANCOVA approach was chosen as it has been shown to give robust results even when variables are not normally distributed [17].

A $P < 0.05$ was considered to be statistically significant. All analyses were performed using SPSS version 26 (IBM-SPSS, Chicago, IL, USA).

3. Results

3.1. Participants. From the start of the study, mid-May, until July 1st 2020, a total of 161 hospital employees were included into the study. After applying the abovementioned exclusion criteria, 21 participants were excluded. Additionally, two participants were excluded because they had a performance

of less than 50% rightly signaled targets, 13 participants could not inform their exposure time to COVID-19, and 1 participant did not answer the question about sleep. Of the 124 eligible participants, 80 had substantial and 44 had a minimal exposure to COVID-19. As can be found in Table 1, those in the substantial exposure group had more often a lower level of education, and 11 did not have a bachelor's degree compared to none in the minimal exposure group ($P = 0.014$). Obviously, more participants in the substantial exposure to COVID-19 group had contracted a COVID-19 infection (22.5 versus 9.1%), which was borderline significant ($P = 0.085$). There were no other noteworthy between-group differences.

3.2. Variability of Reaction Times Was Higher in the Substantial Exposure Group. Evaluation of normality showed that reaction time of correct responses and the intraindividual variability of reaction times of correct responses had a normal distribution. Commission and omission errors did not, but as a MANCOVA/ANCOVA approach is robust against violation of normality [17], they can be included in the model. The analyses were corrected for age, sex, sleep quality, education level, previous COVID-19 infection, and profession.

Figure 2(a) shows the mean reaction time, variability of reaction times, and commission and omission errors (Figure 2 and Table 1). The overall MANCOVA reached statistical significance ($F = 2.48$, $df: 4/116$, and $P = 0.048$). The post hoc ANCOVAs showed that intraindividual variability of correct response times was statistically significantly higher in the substantial exposure to COVID-19 group than in the minimal exposure group ($F = 5.83$, $df: 1/116$, $P = 0.017$, and Cohen's $\delta = -0.55$). Although reaction time ($P = 0.075$), the number of omission ($P = 0.126$) and the number of commission ($P = 0.229$) errors were also higher in the substantial versus minimal exposure group, none were statistically significant. To illustrate intraindividual variability of correct response times, we selected 2 participants (one from each group) and plotted their reaction times in Figure 3. The participant from the minimal exposure group (blue) had a mean reaction time of 370 ms and a mean intraindividual variability of correct response times of 52 ms, whereas the participant from the substantial exposure group (red) had a mean reaction time of 390 ms with an intraindividual variability of correct response times of 96 ms. As can be seen in Figure 3, for a lower mean intraindividual variability of correct response times, the individual reaction times tend to center more around the mean, whereas for a high intraindividual variability of correct response times, the reaction times show a larger spread.

As the higher reaction time in the group with substantial exposure to COVID-19 approached statistical significance, it may partly explain the findings of variability of the reaction times. Therefore, we analyzed the difference in the coefficient of variability of reaction times, which eliminates the influence of reaction time on variability of reaction times [14, 15]. As can be found in Table 1, the coefficient of variability was higher in the substantial exposure group ($F = 4.23$, $df: 1/116$, $P = 0.042$, and Cohen's $\delta = 0.56$). This demonstrates

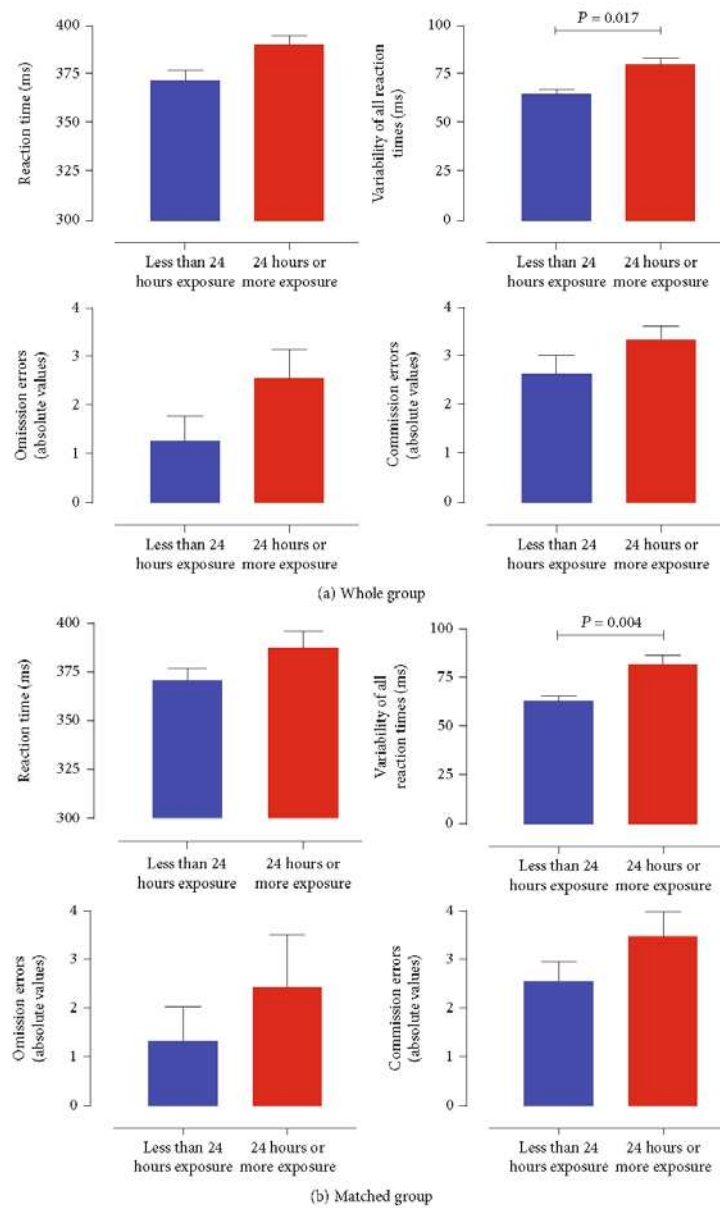


FIGURE 2: (a) Bar graphs of the mean reaction time of the correct responses, mean variability of all reaction times of the correct responses, and mean omission and commission errors with standard error of the mean of the analysis with all participants included. (b) Bar graphs of the mean reaction time of the correct responses, mean variability of all reaction times of the correct responses, and mean omission and commission errors with standard error of the mean of the analysis of both groups matched for size. Blue bars depict participants with minimal COVID-19 exposure, and red bars represent those with substantial exposure to COVID-19 patients.

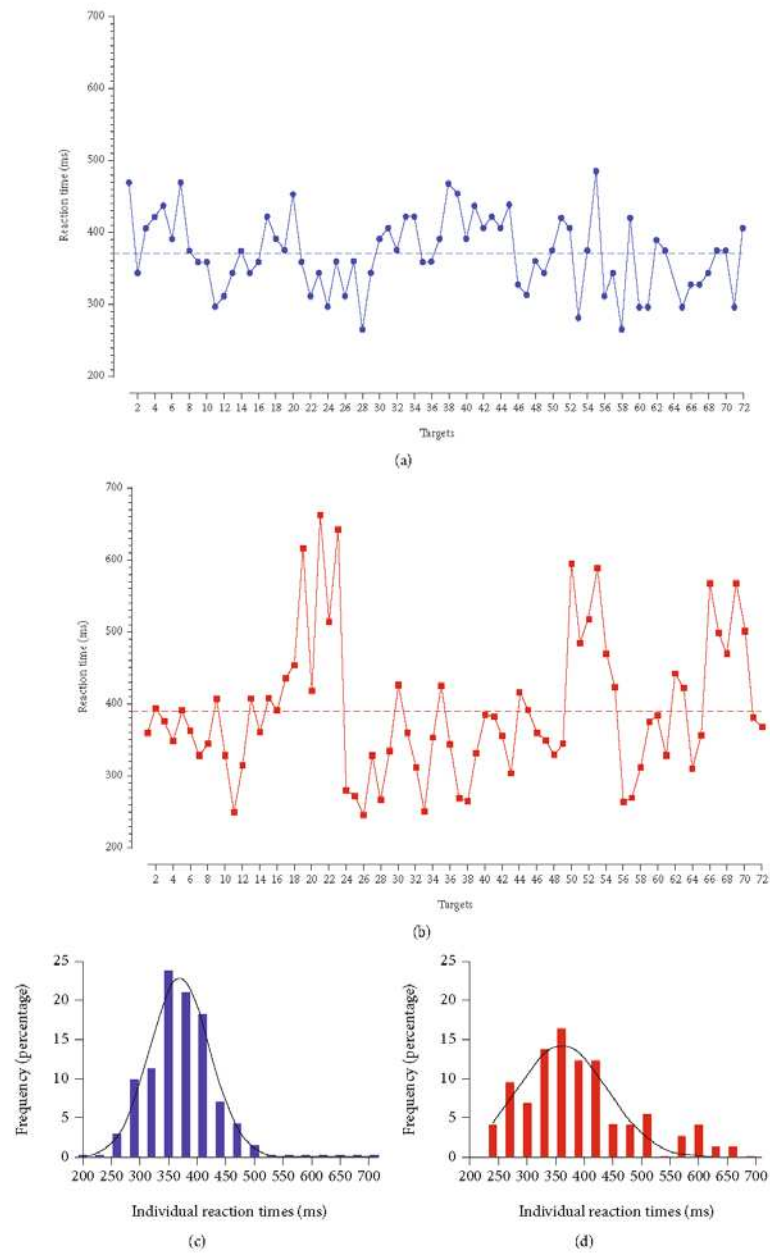


FIGURE 3: Graph of two typical participants, one in the minimal exposure group (blue circles), and one in the substantial exposure group (red squares). Both have a similar mean reaction time as represented by the dashed lines, but their variability of reaction times was different (blue: 52 ms versus red: 96 ms). Below, a histogram of all reaction times with Gaussian curve is plotted, clearly showing a wider and lower curve for the participant in the 24 hours or more exposure group, indicative of larger variability in reaction times.

TABLE 2: Group characteristics of the matched groups.

	Minimal exposure to COVID-19	Substantial exposure to COVID-19	P value
N	32	32	-
Age (years)	39.06 ± 9.47	40.84 ± 8.47	0.431
Sex (male/female; % male)	9/23 (28.1)	8/24 (25.0)	0.999
Education level			0.113
Elementary level (%)	0 (0.0)	1 (3.1)	
High school level (%)	0 (0.0)	3 (9.4)	
Bachelor or higher (%)	32 (100.0)	28 (87.5)	
Exposure time to COVID-19 (%)			-
5 hours or less	22 (68.8)	-	
6 to 11 hours	7 (21.9)	-	
12 to 23 hours	3 (9.4)	-	
24–35 hours	-	8 (25.0)	
36–47 hours	-	16 (50.0)	
48 or more hours	-	8 (25.0)	
Self-reported poor sleep quality (last 2 weeks)			0.910
Never	7 (21.9)	9 (14.1)	
Less than a week	12 (37.5)	11 (34.4)	
More than a week	3 (9.4)	4 (12.5)	
Almost all days	10 (31.3)	8 (25.0)	
Previous COVID-19 infection (%)	4 (12.5)	10 (31.1)	0.129
Profession*			0.430
Medical/paramedical (%)	19 (59.4)	23 (71.9)	
Other (%)	13 (40.6)	9 (28.1)	
Attentional performance			Cohen's δ
Reaction time (ms)	370.61 ± 35.88	387.57 ± 46.87	-0.41
Variability of reaction time (ms)	63.44 ± 14.16	82.10 ± 29.99	-0.81
Coefficient of variability	0.171 ± 0.035	0.212 ± 0.064	-0.81
Omission errors (min-max)	0 (0–21)	0.50 (0–31)	-0.22
Commission errors (min-max)	2 (0–10)	3 (0–10)	-0.36

Data are presented as mean with standard deviation, as absolute numbers with percentages between parentheses, or as absolute numbers with the minimum and maximum values. *Medical and paramedical professions included medical doctors and medical residents, nurses, physiotherapists, and psychologists. Other professions included nutritionists, pharmacists, engineers, and administrative, security, and laboratory employees.

that the statistically significant difference found for variability of reaction times was not driven by a difference in reaction times itself.

3.3. Previous COVID-19 Infection Did Not Affect Performance. An infection with COVID-19 may affect cognitive and attentional performance. Therefore, we have used this variable as a confounding factor. Additionally, we repeated the MANCOVA removing the 22 participants (4 in the minimal and 18 in the substantial exposure group) from the analyses. Despite the loss of degrees of freedom and potential statistical power, the overall MANCOVA remained statistically significant ($F = 3.40$, $df: 4/95$, and $P = 0.012$), with variability of reaction times ($F = 6.88$, $df: 1/95$, $P = 0.010$, and Cohen's $\delta = 0.62$) and the coefficient of variability ($F = 5.67$, $df: 1/95$, $P = 0.019$, and Cohen's $\delta = 0.55$), being the only variables reaching statistical signifi-

cance. This indicates that a previous infection of COVID-19 did not have a major effect on the here presented results.

3.4. Variability of Reaction Times Remains Higher after Matching Groups for Size. An imbalance in sample size has been found to be able to negatively affect ANCOVA results [18]. Therefore, as an additional analysis, we performed one-on-one matching based on age and sex, including 32 participants in both groups and repeated the ANCOVA for variability of reaction times and the coefficient of variability, correcting for age, sex, sleep quality, education, previous COVID-19 infection, and profession. Table 2 shows the characteristics of these groups, where no differences were noted between them (all $P > 0.05$).

Figure 2(b) shows group performance schematically in a bar graph. The ANCOVAs for both variability of reaction times ($F = 9.06$, $df: 1/56$, $P = 0.004$, and Cohen's $\delta = 0.81$) and the coefficient of variability ($F = 7.52$, $df: 1/56$, $P =$

0.008, and Cohen's $d = 0.81$) remained statistically significant. Excluding those with a previous COVID-19 infection did not alter the results.

4. Discussion

In this study, we set out to identify alterations in attentional functioning, a core cognitive function, in health care professionals with substantial and minimal exposure to COVID-19. Using a brief 90-second Go/No-Go test, we showed that the substantial exposure group exhibited lower attentional performance as compared to the minimal group. In particular, performance was less stable over the duration of the test as evidenced by a significant increase in variability of reaction times in the substantially exposed group as compared to the minimally exposed group. Reaction times and performance accuracy did not reach statistical significance. This finding was robust and not influenced by a previous COVID-19 infection or unequal group size.

Where concepts such as reaction time, commission, or omission errors are relatively straightforward, variability of reaction times may be more difficult to understand. A higher variability indicates that responses during the test show greater fluctuations in reaction times. Translated to our results, it indicates that those with substantial exposure to COVID-19 exhibited larger fluctuations in response times, which is clearly demonstrated in Figure 3. In Figures 3(a) and 3(b), 2 graphs are shown of the reaction time to each target of a participant with minimal (a) and of a participant with substantial (b) exposure to COVID-19. Whereas the dotted line showing the mean reaction time indicates that they were similar between both participants, it becomes clear that the individual reaction times fluctuate more for the participant of the substantial exposure group. For the other participant, the individual reaction times center more around the mean. Indeed, the variability was almost 2 times higher for the participant with substantial exposure than compared to the one with minimal exposure to COVID-19. This is further illustrated in Figures 3(c) and 3(d). The histogram of all reaction times of the participant with minimal exposure (blue) shows a stronger centering around the mean and a more normal distribution than the histogram of the participant with substantial exposure (red).

The clinical and psychological meaning of increased variability in reaction times could not be tested in this study. However, previous studies have demonstrated that variability of reaction times is related to various different (neuro) psychological conditions. For example, higher variability, both in younger and older subjects, was related to worse cognitive functioning in domains including memory, intelligence, and information processing speed [19]. This clearly demonstrates the importance of basic attentional functioning and in this case of variability in reaction times for higher-order cognitive functions, including memory and executive functions. In another study, reaction time was measured in 790 community-dwelling elderly (70+ years of age) using a simple reaction time test. Interestingly, results showed that variability of reaction times was strongly related to increased mortality over 17 years [12]. Moreover, variability

of reaction times remained strongly associated with mortality in a full model, which also included variables such as age, dementia status, smoking, and depression [12]. Additionally, in a large sample of community-dwelling people aged 18 to 85, larger variability in reaction times was both associated with increasing age and with depression [20], and, in another study, higher variability has also been found to discriminate children with ADHD from their peers [21, 22]. Lastly, larger variability of reaction times also seems to be predictive of higher psychological distress, as evidenced by results from the UK Health and Lifestyle Survey [13]. Taken together, it is clear that variability of reaction times has clear psychological, neuropsychological, and clinical importance, and future studies should investigate the longitudinal importance of variability in professionals with different levels of exposure to COVID-19.

The cerebral underpinnings of variability of reaction times have been studied less extensively than those of reaction time itself. In a group of 87 healthy students, variability was linked to EEG recordings and in particular to the P3b event-related potential [23]. The P3b is a subcomponent of the P300 event-related potential and is strongest in the parietal areas, arising around 300 ms after an event [23]. In those students with high variability in reaction times, the latency of the P3b was increased with reduced amplitude, suggesting variability is a measure of noise in neural processing [23]. A functional MRI study using a Go/No-Go task in healthy volunteers showed that increased variability of reaction times was related to an increased response in a network comprising the bilateral middle frontal and right inferior frontal, parietal, and thalamus regions [24]. These regions, falling within the frontoparietal cognitive control network, have been found in other studies as well [25]. This network has been linked to cognitive control of behavior and monitoring of the external environment [26, 27]. Although increased activation in relation to increased variability may seem counterintuitive at first glance, it may suggest that greater top-down executive control is necessary in the case of higher variability [24]. The cerebral correlates could not be studied in the current preliminary assessment, but should be included to evaluate structural and functional cerebral involvement in reaction time performance in health care professionals exposed to COVID-19.

Interestingly, the increase in variability of reaction times was not accompanied by an increase in omission or commission errors, which indicates that the lapses in attention were not mirrored by lower accuracy. One can speculate that our group with substantial exposure to COVID-19 was capable of keeping up performance on a basic and easy to perform Go/No-Go task. Whether this holds true for, for example, work-related functions could not be determined in this study. Alternatively, because of the short duration of the test, the possibility of commission errors was with 20% relatively low, compared to an 80% chance of making omission errors. This methodological difference may have prevented us from finding a higher error rate in the substantial exposure to COVID-19 group. Future studies using longer versions of Go/No-Go tasks need to be used to determine the effect of exposure to COVID-19 on accuracy.

Some studies seem to indicate that having had a COVID-19 infection can negatively influence cognitive performance [28], although more studies are needed. As the number of previous COVID-19 infections is nonsignificantly higher in the group substantial exposure to COVID-19, this could in part explain our findings. Therefore, we have used previous COVID-19 infection as a confounding factor, which did not alter the results. In a secondary analysis, we excluded the participants with a previous COVID-19 infection and reran the analyses. Again, variability of reaction times remained statistically significantly higher in the substantial exposure to COVID-19 group relative to the minimal exposure group. This indicates that our results may not be driven by a previous COVID-19 infection.

In the current study, intraindividual variability of reaction time was defined as the standard deviation of all individual reaction times associated with correct responses to the target. Previous investigations using reaction-time tasks have suggested that these distributions can also be fitted by ex-Gaussian distributions [29]. Ex-Gaussian distributions are described by the convolution of a normal distribution and an additional exponential function [30]. This gives three independent parameters, μ that represents the mean of the normal component, σ , which corresponds to the standard deviation of the normal component, and τ that corresponds to the variability of the exponential function [31]. However, our data demonstrate that the sample means are independent of the standard deviations, which gives support for the assumption of a Gaussian distribution of the reaction time data. In addition, a previous study, comparing multiple measures of variability, including the standard deviation, found that all produced similar results and were related to clinical features [32].

The number of targets and nontargets determines the reliability of measures of reaction time, variability of reaction time, and accuracy. The here used test consisted of 72 targets and 18 nontargets. Previous studies have shown that both reaction time and variability of reaction time can be reliably measured by tests as short as 52 seconds with 20 items [29, 33, 34]. In that regard, the here used 90-second CVAT has sufficient targets to reliably measure reaction time and variability of reaction time. Regarding accuracy, with 72 targets, the possibility for omission errors is relatively high. This, however, is at the expense of commission errors, as the possibility of false positive responses is limited to 18. Consequently, the use of the 90-second CVAT may have decreased the possibility to capture accuracy alterations.

A commonly used measure related to accuracy is d' , which represents the sum of the normalized commission and omission errors. To calculate this measure, it is imperative that there are sufficient targets and nontargets allowing for participants to make mistakes. As a consequence of the lower number of targets and especially of nontargets in the Go/No-Go task used in this study, we were less capable of capturing accuracy. Therefore, it was not possible to reliably calculate d' in this study, but future studies using Go/No-Go tasks of longer duration should consider including d' .

Strengths of this study include the well-matched groups who were free of many factors that could influence Go/No-Go performance, such as poor sleep quality, certain types of medication, and fatigue associated with long work hours, and the inclusion of health care workers who do not have a medical profession. However, no information on symptoms of depression, anxiety, or burnout was available in this study. Furthermore, neuroimaging was not collected, which inhibits a better understanding of the neural correlates of the Go/No-Go task in this sample. Due to the short time of the test and the nonjittered stimulus presentation time, it cannot be ruled out that some participants at some point showed automated responses. However, as all participants completed the test for the first time, automated responses are less likely. Because most participants had either less than 6 or more than 36 hours of exposure time to COVID-19, it was not possible to perform an ordinal regression analysis to evaluate the effects of exposure time in the other groups. Therefore, we opted for performing a MANCOVA. To exclude the effect of fatigue on performance, we excluded those who participated after their shift. However, future studies could adopt a pre- and post-shift design, in order to address the question about fatigue in a better way.

In conclusion, we demonstrated that hospital employees with substantial exposure to COVID-19 have a profile of reaction time performance that fluctuates more, i.e., is less stable, as compared to their counterparts with minimal exposure. However, there were no significant differences in test accuracy or in reaction time itself. Whether the variability in reaction times in the substantially exposed group is related to a greater risk of an accidental SARS-CoV-2 infection, other work complications, or greater cognitive or psychological burden needs to be determined in future studies. Future research should, furthermore, focus on the interaction between psychological distress, well-being, fatigue, and attentional functioning in this group ultimately, to be able to better assist those in need of (psychological) counseling.

Data Availability

Data is available from the corresponding author upon reasonable request.

Conflicts of Interest

No conflicts of interest pertaining to this study were reported.

Authors' Contributions

EvD participated in data collection and analysis and wrote the manuscript. GJS participated in the writing of the manuscript. SGA participated in the design of the study and critically revised the manuscript. ALTG, CRM, ACM, ACF, and JCT participated in the design of the study, in data collection, and critically revised the manuscript. PRYF was responsible for recruitment of the participants and critically revised the manuscript. SLS participated in the design of the study, in data collection and analysis, and wrote the manuscript.

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APÊNDICE B - Artigo publicado “*Spirituality as a protective factor for chronic and acute anxiety in Brazilian healthcare workers during the COVID-19 outbreak*”

PLOS ONE

RESEARCH ARTICLE

Spirituality as a protective factor for chronic and acute anxiety in Brazilian healthcare workers during the COVID-19 outbreak

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Abstract

Background

Anxiety symptoms (AS) are exacerbated in healthcare workers (HCWs) during the COVID-19 pandemic. Spirituality is known to protect against AS in the general population and it is a construct that differs from religion. It can be assessed using structured questionnaires. A validated questionnaire disclosed three spirituality dimensions: peace, meaning, and faith. In HCWs we investigated the predictors of chronic anxiety (pre-COVID-19 and during the pandemic) and acute anxiety (only during the pandemic), including spirituality in the model. Then, we verified which spirituality dimensions predicted chronic and acute anxiety. Lastly, we studied group differences between the mean scores of these spirituality dimensions.

Material and methods

The study was carried out in a Brazilian Hospital. HCWs (n = 118) were assessed for spirituality at a single time-point. They were also asked about AS that had started pre-COVID-19 and persisted during the pandemic (chronic anxiety), and AS that had started only during the pandemic (acute anxiety). The subjects without chronic anxiety were subdivided into two other groups: acute anxiety and without chronic and acute anxiety. Forward stepwise logistic regressions were used to find the significant AS predictors. First, the model considered sex, age, religious affiliation, and spirituality. Then, the analysis were performed considering only the three spirituality dimensions. Group means differences in the spirituality dimensions were compared using univariate ANCOVAs followed by T-tests.

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Results

Spirituality was the most reliable predictor of chronic (OR = 0.818; 95%CI:0.752–0.890; $p < 0.001$) and acute anxiety (OR = 0.727; 95%CI:0.601–0.881; $p = 0.001$). Peace alone predicted chronic anxiety (OR = 0.619; 95%CI:0.516–0.744; $p < 0.001$) while for acute anxiety both peace (OR:0.517; 95%CI:0.340–0.787; $p = 0.002$), and faith (OR:0.674; 95%CI:0.509–0.892; $p = 0.006$) significantly contributed to the model. Faith was significantly higher in subjects without AS.

Conclusion

Higher spirituality protected against chronic and acute anxiety. Faith and peace spirituality dimensions conferred protection against acute anxiety during the pandemic.

Introduction

Anxiety symptoms (AS) are frequently associated with physical and mental illnesses [1–3]. Age and sex are reliable predictors of AS [4–9]. Furthermore, some studies have reported a protective effect of spirituality on AS in the general population [10–16]. Spirituality can involve cognitive and emotional states such as beliefs, motivations, and a sense of gratitude [17–19]. In particular, positive cognitive or emotional aspects of spirituality have been found to be associated with less anxiety [18]. Moreover, González-Sanguino et al., using regression methods, have demonstrated the importance of spirituality as the main protector against the appearance of AS [15].

Previous investigations have shown that AS are exceptionally high in healthcare workers (HCWs) [20]. Given the potential protection of greater spirituality against anxiety [12–16] and the high prevalence of AS among HCWs [20–22], it would be interesting to investigate spirituality as a protector of AS in this specific population. However, the effect of spirituality on AS has not been systematically investigated in HCWs.

During the COVID-19 outbreak, AS have been found to be exacerbated among HCWs worldwide [21–26]. In Brazil, the current pandemic has massively impacted HCWs with a high prevalence of AS [27–29]. A previous cross-sectional study conducted among Brazilian HCWs during the first six months of 2020 showed that most of them experienced a high level of anxiety [27]. Villela et al. also found that the pandemic had a crucial impact on HCWs' work routines, with a high rate of AS [28]. It is noteworthy that spirituality research in Brazil has great relevance due to its cultural context since spirituality and religion are commonplace within Brazilian culture [30, 31]. Indeed, most of the Brazilian population has a religious affiliation [31]. To our knowledge, the relative importance of the potential spirituality protective effect on AS has not been studied among Brazilian HCWs in the current pandemic.

Spirituality encompasses a broader sense of inner peacefulness or harmony, a search for meaning and purpose of life, and how an individual experiences his or her faith [32–34]. It can be measured using well-validated instruments, such as the Functional Assessment of Chronic Illness Therapy-Spiritual Well-being (FACIT-Sp) [35–37]. The FACIT-Sp measures overall spirituality and three psychologically meaningful dimensions: peace, meaning, and faith [36, 38]. These spirituality domains are considered as separate constructs that make up spiritual well-being [37, 39]. Another highlighted aspect is that this multifactorial construct differs from religion [39, 40].

In times of distress, it could be hypothesized that a higher spirituality could predict lower AS in HCWs who are submitted to stressful work situations. Besides, the protection given by the different spirituality dimensions against AS may depend on the moment these symptoms begin. A feeling of peace reflecting an affective dimension of spirituality [35, 36, 41, 42], and it has been associated with mental health [35, 38, 43]. Then, we hypothesized that peace dimension would be a predictor of AS in HCWs who anxiety started before and persisted during the pandemic (chronic anxiety) and those whose anxiety started only during the pandemic (acute anxiety). Given that personal faith can increase psychological resilience [44, 45], we hypothesized that faith would reach the highest score in those without chronic and acute anxiety. In addition, as faith is associated with better coping in stressful times [46–48], we also hypothesized that higher personal faith could be a predictor of less acute anxiety during the pandemic. Therefore, the potential protective effect of spirituality, and its dimensions on AS should be studied in chronic and acute anxiety. However, the effects of each spirituality dimension on the AS among HCWs have not been studied during the COVID-19 outbreak.

The present study aimed to investigate chronic and acute anxiety in HCWs, including spirituality and its dimensions. Firstly, we assessed the AS predictors of chronic. Secondly, we studied the AS predictors of acute anxiety during the pandemic. Thirdly, for chronic and acute anxiety, we analyzed which spirituality dimensions would predict AS. Fourthly, we investigated the differences among all the groups (chronic anxiety, acute anxiety and without chronic and acute anxiety), considering the mean scores of the spirituality dimensions that were found to be significant predictors of AS according to the third objective.

Materials and methods

This observational study was carried out in HCWs from May 12th until July 10th 2020 at a reference Tertiary Hospital for COVID-19 in Rio de Janeiro, Brazil. We included the HCWs of both sexes with ages ranging from 20 to 60 years old. Exclusion criteria: previous or current neurological disorders, uncontrolled clinical conditions, and taking antidepressant, anxiolytic, and antipsychotic medications.

The HCWs who were working in the Hospital during the period of this research were invited to participate in the present study. The researcher explained the study aims and the procedure of data collection. Those who verbally consented to take part in the study were given the questionnaire. The subjects were informed that they could withdraw from the study at any time and return the questionnaire. They were left free to ask questions and to obtain explanations. They all signed the written informed consent.

All filled out a face-to-face questionnaire about spirituality and AS. The presence of AS was assessed in an all-or-none fashion based on a questionnaire that included a question if these symptoms had persisted for a minimum of 6 months. As the first case of COVID-19 in Brazil was reported on February 26th 2020, it was possible to identify the participants who presented AS that started before and persisted after this date (chronic anxiety). Then, the sample was divided into two groups according to the presence of AS that had started before COVID-19 and persisted during the pandemic (no chronic anxiety vs. chronic anxiety groups)—first objective. In order to assess the AS directly associated with the pandemic period, we subdivided the sample without anxiety before the pandemic (no chronic anxiety group) into two other groups: subjects that remained without AS all the time (without chronic and acute anxiety group) and those who started AS only during the pandemic (acute anxiety group)—second objective.

Spirituality was assessed through the FACIT-Sp [35, 36, 41, 49, 50]. This scale is a widely used instrument in clinical research to measure spirituality and validated for the Brazilian

population [51, 52]. The FACIT-Sp items emphasize a sense of peacefulness, harmony, meaning or purpose in life, strength and comfort from one's faith or spiritual beliefs [35, 36, 38]. It is a self-administered questionnaire composed of 12 items, divided equally between three dimensions: peace (items 1, 4, 6, and 7), meaning (items 2, 3, 5, and 8), and faith (items 9, 10, 11, and 12). The participant was instructed to indicate how true an affirmative had been for them during the past seven days, using a 5-item response format ranging from not at all (0) to very much (4), except for items four and eight, which must be reverse coded. Total scores range from 0 to 48, with higher scores indicating higher spiritual well-being. The questionnaire also provides scores per dimension. Previous studies have demonstrated the validity and reliability of the FACIT-Sp among Brazilians, e.g., Pereira & Santos (2011) [51] and Luchetti et al. (2013) [52]. These studies have shown good psychometric properties for the Portuguese version of FACIT-Sp, such as high reliability and adequate construct validity [51, 52]. In the present study, the internal reliability of the FACIT-Sp was high [Cronbach's alpha (α) = 0.823]. Concerning each spirituality dimension, the Cronbach alphas for the peace, meaning, and faith were 0.865, 0.828, and 0.894, respectively.

For the statistical analysis, quantitative variables were reported as absolute and relative frequencies. The normality of variables was confirmed by assessing the histograms, QQ plots, and Kolmogorov-Smirnov test. Normally distributed continuous variables (age and FACIT-Sp total score) are presented as means and standard deviations and were evaluated using independent *t*-tests. The associations are presented as odds ratios (OR) and 95% confidence intervals (CI 95%).

In the whole sample, a forward stepwise binomial logistic regression was used to predict whether participants could be correctly classified according to the presence or absence of AS that started before the COVID-19 and persisted during the pandemic (chronic anxiety group)—first objective. In order to investigate the acute anxiety, we selected only those participants without AS before the pandemic. They were divided into those who remained without AS (without chronic and acute anxiety group) and those who started AS during the COVID-19 outbreak (acute anxiety group). In this subsample, we also investigated the reliable predictor(s) of acute anxiety (second objective). We used the forward stepwise regression method to find the predictors that could contribute significantly to the model. Our model considered sex, age, religious affiliation, and the FACIT-Sp total score for both analyses. We intended to investigate whether these variables could significantly predict less AS among HCWs. Nagelkerke R^2 was calculated to estimate the explained variance of the dependent variable, and the Wald test was used to determine the statistical significance of each predictor. The stepwise forward selection included only predictors significant to the model at a probability of F ($p < 0.05$). For both the entire sample and the subsample, forward stepwise logistic regressions were used to determine which spirituality dimensions would predict AS (third objective).

To assess the effect of group (chronic anxiety, acute anxiety, and without chronic and acute anxiety groups) on the spirituality dimensions that were found to predict the presence of AS (forth objective), a MANCOVA was performed to examine group differences on those spirituality dimensions, using age, sex, and religious affiliation as covariates. In the case of a significant overall MANCOVA, post-hoc ANCOVAs for each dependent variable (spirituality dimensions) were checked for statistical significance. In the case of significant ANCOVAs, post-hoc *T*-tests assessed the presence of significant group differences for each spirituality dimension. Multiple comparisons were correct by the Bonferroni method. For the MANCOVA and each of the ANCOVAs, the η^2 (Eta-squared) was computed to calculate the effect size of the results. Cohen has suggested that $\eta^2 = 0.01$ should be considered a small effect size, 0.06 a medium effect size, and 0.14 a large effect size [53].

For all the tests, significance was set at a p -value < 0.05 . SPSS Statistics for Windows, version 25.0 (IBM Corp, 2017), was used for statistical analyses.

The local Research and Ethics committee approved this study (number: 39365120.8.0000.5258) in accordance with the Declaration of Helsinki. Participation in this study was voluntary without monetary or non-monetary compensation. HCWs were invited to take part in this study voluntarily. All of them were informed about the study aims and the entire procedure of data collection. Subjects were assured that all data collected during the research process would be treated confidentially. The volunteers provided written informed consent. They could withdraw from the study at any time by declining to fill in the questionnaire. During the data collection, a researcher was available if any doubts or questions emerged.

Results

Predictors of chronic anxiety (first objective)

One hundred and forty-seven were invited, but eight did not agree to participate in this study. Therefore, the initial sample has consisted of 139 subjects. From this sample, 21 were excluded because they reported the use of psychotropic medications. Then, the whole final study sample consisted of 118 subjects. The age ranged from 22 to 60 years (41.9 ± 10.3), and the majority was female ($n = 79$; 66.9%). Most participants (64.4%) had a religious affiliation. Seventy-two participants (61%) reported chronic anxiety. The FACIT-Sp mean score was statistically higher for the no chronic anxiety group (38.6) as compared to the chronic anxiety group (31.6) [$t(116) = 6.0$; $p < 0.001$] - [S1A Fig](#) and [Table 1](#).

The model included sex, age, religious affiliation, and the FACIT-Sp total score as predictors of chronic anxiety. Spirituality (FACIT-Sp total score) was the only significant predictor in the forward stepwise regression (OR = 0.818; 95% CI: 0.752–0.890; $p < 0.001$). This model was statistically significant [$\chi^2(1) = 33.2$; $p < 0.001$], explaining 33.2% (Nagelkerke R^2) of the variance and classifying correctly 71.2% of the cases.

Table 1. Descriptive statistics of the variables used as predictors for the three groups: Anxiety that started pre-COVID-19 and during the pandemic (chronic anxiety), anxiety that started only during the pandemic (acute anxiety), and without chronic and acute anxiety group.

First Objective	No chronic anxiety (n = 46)	Chronic anxiety (n = 72)	p-value
Sex female, n (%)	27 (58.7%)	52 (72.2)	0.2
Age (Years), Mean (SD)	45.4 (10.4)	39.7 (9.5)	0.003
Religious affiliation, n (%)	29 (63.0)	47 (65.3)	0.8
FACIT-Sp (score), Mean (SD) *	38.6 (4.5)	31.6 (6.9)	<0.001
Second objective	Without chronic and acute anxiety (n = 21)	Acute anxiety (n = 25)	p-value
Sex female, n (%)	11 (52.4)	16 (64.0)	0.6
Age (Years), Mean (SD)	46.4 (11.5)	44.6 (9.5)	0.6
Religious affiliation, n (%)	12 (57.1)	17 (68)	0.5
FACIT-Sp (score), Mean (SD) ^b	41.3 (3.9)	36.2 (3.7)	0.001

Abbreviations: HCWs = healthcare workers; AS = anxiety symptoms; SD = standard deviation; p = proof value; OR = Odds Ratio; CI = confidence interval.

* The FACIT-Sp score was the most reliable predictor of chronic anxiety in the forward stepwise regression method (OR = 0.818; 95% CI: 0.752–0.890; $p < 0.001$)

^b The FACIT-Sp score was the most reliable predictor of acute anxiety during the pandemic in the forward stepwise regression method (OR = 0.727; 95% CI: 0.601–0.881; $p = 0.001$).

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Predictors of acute anxiety (second objective)

To investigate the relationship between spirituality and acute anxiety during the current outbreak, we selected all subjects without AS starting before the pandemic ($n = 46$). Of these 46 participants, 25 (54.3%) started AS only during the pandemic (acute anxiety group), and 21 continued without AS (without chronic and acute anxiety group). In this subsample, the FACIT-Sp total mean score was statistically higher in participants that remained without AS (41.2) as compared to acute anxiety group (36.2) [$t(44) = 4.4$; $p < 0.001$]—[S1B Fig](#) and [Table 1](#).

The model included sex, age, religious affiliation, and spirituality (FACIT-Sp total score). Spirituality was the only significant predictor of acute anxiety in the forward stepwise regression (OR = 0.727; 95% CI: 0.601–0.881; $p = 0.001$). This model was statistically significant [$\chi^2(1) = 13.6$; $p < 0.001$], explaining 38.5% (Nagelkerke R^2) of the variance and classifying correctly 69.6% of the cases.

Dimensions of spirituality (third objective)

Peace was the only predictor of chronic anxiety (OR = 0.619; 95% CI: 0.516–0.744; $p < 0.001$). This model was statistically significant [$\chi^2(1) = 40.4$; $p < 0.001$], explained 39.3% of the variance, and classifying correctly 78.8% of the cases—[S2A Fig](#).

Both peace (OR: 0.517; 95% CI: 0.340–0.787; $p = 0.002$) and faith (OR: 0.674; 95% CI: 0.509–0.892; $p = 0.006$) dimensions predicted acute anxiety—[S2B Fig](#). This model was statistically significant [$\chi^2(2) = 23.4$; $p < 0.001$], explained 53.3% of the variance, and correctly classified 76.1% of the cases.

Comparison of spirituality dimensions that were predictors of anxiety (fourth objective)

After adjusting for age, sex, and religious affiliation, the MANCOVA showed a significant effect of group (chronic anxiety, acute anxiety, and without chronic and anxiety group) on peace and faith dimensions ($F = 15.3$, $df = 4/222$, $p < 0.001$, $\eta^2 = 0.216$). The univariate tests showed that group affected peace ($F = 29.1$, $df = 2/112$, $p < 0.001$, $\eta^2 = 0.342$), and faith ($F = 5.4$, $df = 2/112$, $p < 0.006$, $\eta^2 = 0.88$). The t -tests showed significant means differences in all comparisons for the peace dimensions. Regarding the faith dimension, the mean scores were significantly higher in the without chronic and acute anxiety group compared to the chronic anxiety and acute anxiety groups.

Discussion

We found a high prevalence of AS in HCWs. Our findings are in line with recent studies on the frequency of AS in HCWs [[23](#), [24](#), [54](#), [55](#)]. Additionally, we reported a high rate of acute anxiety (54.3%) during the pandemic. These data may reflect the specific psychological impact of COVID-19 on HCWs.

Spirituality was the most reliable predictor of acute and chronic anxiety. We showed that the peace spirituality dimension was a significant predictor of less AS among HCWs irrespective of whether these symptoms were chronic or acute during the pandemic. Moreover, the faith dimension significantly predicted AS that started only during the pandemic. This finding indicates the importance of personal faith as an additional protective factor for acute anxiety in the current outbreak.

Predictors of chronic anxiety (first objective)

We used the forward stepwise regression method to find the best predictors of the AS. The stepwise forward selection included only predictors that enhanced the significance of the

model at a probability of F ($p < 0.05$). Based on this approach, sex, age, and religious affiliation were not included as predictors in the logistic regression model (forward regression method). Using this method, the spirituality variable was enough to predict AS adequately. Our results about religion probably reflect that religious affiliation is a construct that is conceptually different from spirituality [39, 40].

The present data revealed that high spirituality protects against chronic anxiety. This is supported by other studies that have shown the association between greater spiritual well-being and lower AS in the general population [15, 16, 56].

The FACIT-Sp mean scores were 38.6 and 31.6 in no chronic and chronic groups, respectively. As a FACIT-Sp score above 36 points has been considered high spiritual well-being [57, 58], we inferred that most subjects in the no chronic group had high spirituality based on this cutoff.

Predictors of acute anxiety (second objective)

Spirituality was showed to be the only reliable predictor of acute anxiety. As there is an increase in the number of subjects with anxiety in times of distress, it is conceivable that higher spirituality should be needed to overcome the demands of a new stressful situation. The FACIT-Sp mean score in the group without chronic and acute anxiety reached 41.3 points, well above the 36 points (the limit for a high spirituality) [57, 58]. In contrast, the FACIT-Sp score was below this cutoff point in most subjects of the acute anxiety group. As described for chronic anxiety, greater spiritual well-being also protected against acute anxiety during the pandemic.

The effect of spirituality on chronic and acute anxiety (first and second objectives)

We demonstrate the impact of spiritual well-being among HCWs in chronic and acute anxiety (first and second objectives). High spirituality involves positive emotions and spiritual beliefs, which may provide a better psychological adaptation against AS [18]. Another possible reason is that spirituality has been shown to be a consistent resilience factor [59]. As a higher spirituality was the most reliable predictor of less acute anxiety, we can infer that HCWs with increased spiritual well-being tend to develop internal mechanisms that help them cope with the adversities associated with the current pandemic.

A potential mechanism for spirituality protection on AS could be related to the neurobiological substrates of spirituality [60–63]. Although multiple brain regions may contribute to spirituality, the parietal cortex is arguably the most frequently implicated brain region related to spirituality [63]. Furthermore, the medial parietal region appears functionally connected with lateral areas of the parietal cortex associated with self-reference or a felt sense of connection outside of oneself [64]. Rim et al. (2019) systematically reviewed the relationship between spirituality and electroencephalography, structural and functional neuroimaging [65]. This and others studies have demonstrated several brain regions associated with spiritual well-being, such as parietal cortex, medial frontal cortex, orbitofrontal cortex, precuneus, posterior cingulate cortex, default mode network, and caudate [63, 65–67].

Effect of the spirituality dimensions on AS (third objective)

The peace dimension of spirituality was the only significant predictor of chronic anxiety. Our results agree with previous studies in different populations, in which the sense of peace was associated with less AS [11, 68, 69]. This finding can be explicated because the peace subscale is an affective expression of spirituality, reflecting a sense of inner harmony [35, 36, 41, 42],

and this dimension has been specifically related to mental health [35, 38, 43]. However, feeling at peace alone did not protect against the acute anxiety during the current outbreak. We found that a high faith score was also necessary to protect against acute anxiety during the pandemic. This result may indicate that when HCWs cope with anxiety triggers during the pandemic, their faith is important to reduce AS.

It should be mentioned that personal faith is more subjective and deeper than religious affiliation [40, 70]. Our finding may have some possible explanations. First, faith can be a source of hope for the future [45, 47, 71]. Second, faith can provide an optimistic worldview [44, 72], which is inversely associated with AS. Finally, cultivating expressions of faith can increase psychological resilience [45] and, consequently mitigate AS [73].

Taken together, it is possible that a sense of inner peace or harmony and, especially, personal faith have served to better coping with stress in the face of uncertainties associated with the pandemic.

Comparison of spirituality dimensions that were predictors of anxiety (fourth objective)

As expected, the subjects without chronic and acute anxiety presented the highest mean score for inner peace. The peace dimension was greater in acute anxiety as compared to chronic anxiety. This finding may indicate that mental health was better in the subjects without chronic anxiety.

Regarding the faith dimension, HCWs without anxiety had significantly higher faith scores compared to those with chronic and acute anxiety. These data suggest possible protection of faith against AS in this specific population. In particular, our results highlighted the role faith played in the pandemic. Only the group of HCWs with the highest faith protection could remain without AS during the pandemic. This finding supports the relevance of faith as a predictor for better psychological coping to the current COVID-19 outbreak.

Limitations, strengths, and future directions

A limitation of the present study is the small number of subjects in the subsample of HCWs. Although the HCWs of the present study can be considered a representative sample of Brazilian HCWs, future studies should be conducted in a larger sample of HCWs recruited from various areas in Brazil. A strength is that the questionnaires were applied face-to-face by the researchers since most previous studies were carried out by e-mail, social media, or online websites.

A practical implication of our findings is that it would be useful to promote enhanced screening for AS and address spirituality in HCWs, particularly during stressful times. Studies of medical and psychiatric patients report that the majority have spiritual issues, and most of those needs currently go unmet [33, 39, 74]. Therefore, health professionals may engage HCWs in a dialogue that allows them to talk about their spirituality. Additionally, based on the present study, it may be useful to take spiritual assessments during the inclusion of HCWs in preventive and therapeutic mental health programs.

From a public health perspective, future research should focus on potential interventions based on spirituality in HCWs. In other populations, psychosocial interventions have proved effective in improving spirituality [75–78], such as spiritually integrated psychotherapy [79, 80], yoga [78], and meditation [78, 79]. In addition, a previous meta-analysis found that faith-adapted cognitive-behavioral therapy (CBT) may outperform both control conditions and standard CBT in the treatment of anxiety [81]. Our data highlight the protective role of faith and inner peacefulness. Therefore, psychosocial interventions in HCWs during the pandemic

should consider these two spirituality dimensions. These approaches may lower the impact of anxiety triggers on HCWs.

Conclusions

The present study shows that spirituality can be considered a protective factor against AS in HCWs, irrespective of whether the symptoms started before and during the pandemic. This finding suggests that HCWs with high spiritual well-being tend to develop internal mechanisms that help them cope with psychological stress.

Additionally, we found that spirituality dimensions influenced the AS differently according to the starting time of symptoms. Peace spirituality dimension was the best predictor of acute and chronic anxiety, whereas the faith dimension emerged together with peace to confer protection on acute anxiety starting during the COVID-19 outbreak. These data suggest that a personal faith can represent an important coping strategy facing a severe stressful moment among HCWs. Therefore, interventions based on improving spiritual well-being and considering these spirituality dimensions could be designed and implemented in HCWs.

Supporting information

S1 Fig. The mean FACIT-Sp total score for each group. (A) FACIT-Sp total score is statistically significantly higher in the no chronic anxiety group compared to the chronic anxiety group (* $p < 0.001$), indicating a lower spirituality among the subjects experiencing anxiety that started pre-COVID-19 and during the pandemic (B) The boxplot indicates that the FACIT-Sp total score is also statistically significantly higher in the group without chronic and acute anxiety (* $p < 0.001$) as compared to the acute anxiety group.
(TIFF)

S2 Fig. Effects of spirituality dimensions on anxiety symptoms according to chronic and acute anxiety. (A) The peace was the only spirituality dimension protective of chronic anxiety (B) Peace and faith spirituality dimensions are protective factors against acute anxiety during the pandemic.
(TIFF)

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APÊNDICE C - Artigo publicado “Attention Deficits in Healthcare Workers with Non-Clinical Burnout: An Exploratory Investigation”



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Article

Attention Deficits in Healthcare Workers with Non-Clinical Burnout: An Exploratory Investigation

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Abstract: Burnout syndrome is characterized by exhaustion, cynicism, and reduced effectiveness. Workers with high burnout scores who continue their professional activities are identified as experiencing non-clinical burnout (NCB), which includes early stages where burnout symptoms (BNS) are present but not yet severe enough to necessitate work leave. This study aimed to investigate the impact of BNS on attention performance among healthcare workers (HCWs) at a COVID-19 reference hospital during the pandemic. The Maslach Burnout Inventory (MBI) was applied to assess the three burnout subdomains. The Continuous Visual Attention Test (CVAT) evaluated four different attention subdomains. Participants were divided into two groups based on their scores on the MBI: controls and NCB. Thirteen controls were matched with 13 NCB subjects based on age, sex, and HCW category. This sample ($n = 26$, 65% male) consisted of 11 physicians and 15 nursing professionals with a mean age of 35.3 years (standard deviation = 5.47). NCB subjects had higher impulsivity than controls. There were not any significant group differences in the other attention subdomains. We found significant correlations between impulsivity and all burnout dimensions: higher absolute scores in BNS are associated with higher impulsivity. We concluded that NCB leads to executive attention deficits.

Keywords: burnout; healthcare professionals; attention deficits; impulsivity; executive functions



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1. Introduction

Burnout is considered a consequence of occupational chronic stress and constitutes an important health risk factor among working populations [1]. Burnout consists of three dimensions: exhaustion, cynicism, and reduced personal efficacy. According to Schaufeli and Salanova [2], exhaustion is the depletion of emotional resources, cynicism is related to distancing from work, and reduced personal efficacy is associated with low work self-esteem. Moreover, studies have reported cognitive deficits in workers diagnosed with clinical burnout [3–7]. In this regard, Deligkaris et al. [8] suggested that a cognitive dimension be included in the burnout definition, arguing that burnout has a significant impact on workers' cognitive performance.

A previous study [9] proposed that burned-out individuals can be identified by a high score on the exhaustion scale combined with a highly unfavorable score on at least one of

the two other main components of burnout. Working employees with high burnout scores who keep working are commonly referred to as non-clinical burnout (NCB) employees [10].

NCB represents an early stage of burnout where individuals experience symptoms of exhaustion and depersonalization but continue to work [11]. Initially, NCB manifests as exhaustion and depersonalization, with prolonged exposure to stressors leading to more severe symptoms [10]. Over time, these symptoms escalate, affecting functional abilities and transitioning into clinical burnout [10]. In its clinical form, burnout encompasses emotional and physical exhaustion and depersonalization and includes a reduced sense of personal or professional accomplishment [10]. Additionally, clinical burnout subjects are required to take leave from work [11].

Healthcare workers (HCWs) are usually subjected to a high level of stress [12,13]. High rates of exhaustion were found among HCWs before the pandemic [14,15]. During the COVID-19 pandemic, HCWs were significantly exposed to the risk of virus infection while dealing with patients. Accordingly, recent studies have suggested that exhaustion increased dramatically among HCWs during the COVID-19 pandemic [16–21]. A study in Brazil found that depersonalization and emotional exhaustion were the most affected dimensions in healthcare professionals who were working during the pandemic [22]. Therefore, the presence of burnout symptoms across different HCW roles indicated that this population could provide an adequate sample for the study of cognitive performance in subjects who keep working with high levels of burnout (NCB).

Although cognitive deficits have been described in subjects with clinical burnout, the presence of cognitive impairment among NCB populations remains a matter of controversy. Some studies have shown the presence of cognitive deficits [10] while others have failed to find such impairments [23,24]. If little is known about cognitive impairments in NCB, even less is known when NCB involves HCWs.

However, the study of cognitive performance in HCWs who continued to work with burnout symptoms is of practical and theoretical interest. In practical terms, cognitive problems lead to work-related errors. Experiencing cognitive problems can directly affect work performance, worsening feelings of distress, depression, and anxiety [4,25,26].

In theoretical terms, some authors have suggested the presence of cognitive deficits in NCB. In contrast, others have proposed that compensatory mechanisms can obscure differences in cognitive performance between NCB and controls [27]. For those who advocate the presence of cognitive deficits in NCB, the adverse effects of burnout on cognition might be associated with a decrease of the brain-derived neurotrophic factor, which would disrupt brain functioning and lead to cognitive deficits even in the early stages of burnout [28]. Conversely, two theories are frequently mentioned to explain how NCB employees could cope with cognitive difficulties at work: cognitive reserve and self-regulation theories [29,30]. The cognitive reserve theory suggests that when NCB subjects carry out challenging tasks, they employ new brain networks based on their cognitive reserve processes, allowing them to use other cognitive strategies [29]. The self-regulation theory proposes that NCB employees might still be able to self-regulate and initiate the cognitive reserve to achieve optimal performance because they retain the ability to inhibit prepotent responses and guide their cognitive sources to attain a goal [30].

Several factors, such as the heterogeneity of cognition assessment tools, may underlie the inconclusive findings on cognitive performance and burnout symptoms in NCB subjects. In this regard, the attention domain plays a fundamental role in cognition. Attention is the ability to choose and concentrate on relevant stimuli [31]. In daily life, attention is essential for driving, learning, and performance in several jobs [32,33]. Thus, decreased attentional performance could lead to a higher risk of work-related accidents, as workers might be more prone to make mistakes [33]. Moreover, attention is crucial for adequately function in the other cognitive domains [31,34]. However, attention performance has not been systematically studied in NCB subjects.

Converging lines of evidence suggest that the attention system can be separated into four subdomains: alertness, behavioral inhibition, focused attention, and sustained

attention [35,36]. Intrinsic alertness refers to the internal control of arousal without an external cue, while behavioral inhibition is the ability to control inadequate responses. Focused attention reflects the ability to respond to correct targets, and sustained attention is frequently described as the ability to concentrate over time to detect correct events [31]. Attention subdomains can be reliably measured by Continuous Performance Tests, such as the Continuous Visual Attention test (CVAT) [37–41].

While previous research has acknowledged the cognitive impacts of clinical burnout, our study delves deeper into the attention subdomains in NCB. Therefore, in the present study, we conducted an exploratory investigation of the performance of HCWs working during the COVID-19 pandemic in the CVAT. Specifically, we investigated whether the performance in each attention subdomain was affected in individuals exhibiting NCB. We hypothesized that NCB leads to attention deficits in HCWs.

2. Materials and Methods

2.1. Participants

Volunteers were recruited at a tertiary university hospital in Rio de Janeiro, Brazil, between April and December 2020, during the COVID-19 pandemic. HCWs included medical doctors, nurses, and nurse's aides. First, we performed a brief clinical interview with HCWs aged between 25 and 45 years old. The age lower limit (25 years) was set based on a previous meta-analysis that showed higher rates of emotional exhaustion and depersonalization among younger nurses [42]. As such, younger age might have intensified the symptoms of burnout, whereas advancing age may have functioned as a mitigating factor against burnout. The upper limit of 45 years was chosen based on previous studies that have described a decline in processing speed after 45 years old [43–45]. Accordingly, individuals older than 45 years have higher variability in the scores of the CVAT [46], which could impact the probability of detecting group differences and consequently the need to use larger sample sizes. Then, we applied the following exclusion criteria: use of antipsychotic or antiepileptic medications that might interfere with performance on the CVAT, a history of head trauma with loss of consciousness, current use of alcohol or illicit substances, pre-existing neurological or psychiatric conditions, shift workers, and a past medical record of COVID-19. The exclusion of participants who had COVID-19 was necessary because the infection itself can cause attention impairment [39–41]. All workers were tested at the beginning of their work shifts to exclude fatigue. Based on the Maslach Burnout Inventory (MBI) responses, we established two groups: controls and non-clinical burnout. The classification criteria for these two groups are detailed in the classification subsection (Section 2.2) and were based on the three dimensions of the Portuguese validation of the MBI (Sections 2.2 and 2.4.2). Finally, the selected participants performed the attention task. The experimenter who administered the attention test was blind to the participant's group.

As described by previous authors [7], here it was also difficult to find HCWs with high burnout symptoms who were willing to participate in the study. Thirteen participants with high burnout symptoms (non-clinical burnout group) completed the attentional test. Then, from the remaining 24 participants without burnout symptoms, we selected 13 controls paired by age, sex, educational level, and HCW role. The minimum sample size had been previously determined by a power analysis (Section 2.3).

Participation in this study was voluntary and carried out according to the recommendations of the Research and Ethics Committee of the Federal University of the State of Rio de Janeiro, Brazil (CAAE: 69406817.1.0000.5258), adhering to the Declaration of Helsinki. All subjects gave written informed consent.

2.2. Classification of the Participants Based on Their Maslach Burnout Inventory (MBI) Scores

Burnout can be conceptualized as a continuum, ranging from low to high degrees of the phenomenon. Higher scores in the emotional exhaustion and depersonalization dimensions, and lower scores in the personal accomplishment dimension, are indicative of greater

burnout [47,48]. Some studies have chosen to consider only the emotional exhaustion and cynicism dimensions to diagnose burnout, suggesting that the ineffectiveness dimension (also known as personal accomplishment) reflects a personality pattern [49,50]. Other studies have chosen a one-dimensional criterion (emotional exhaustion), considering that cynicism and low personal achievement would be different phenomena [51].

To classify the subjects according to the presence of significant burnout symptoms (yes or no), we applied the most restrictive criterion as proposed by Brenninkmeijer and collaborators [9], which involves the presence of high exhaustion, high cynicism, and low personal efficacy. We used the cutoff values of the third edition of the MBI manual validated for the Brazilian population. These values are as follows: average EX ≥ 3.2 , average CY ≥ 2.2 , and average PE ≤ 4.0 [52–55].

Here, we also treated burnout as a continuous variable considering the values of each one of the three burnout dimensions. For each participant, we summed the scores obtained in the questions related to a particular dimension. Then, we divided the obtained sum by the number of questions specifically related to that dimension.

2.3. Power Analysis

To estimate the required minimum sample size, we performed a power analysis considering the two different statistical approaches outlined in Figure 1, i.e., mean differences in attention performance between two groups dichotomized according to the presence of burnout symptoms (first approach) and associations between burnout dimensions and attentional performance (second approach). Therefore, two distinct analyses were performed. However, for both conditions, α = Type I error = 0.05 and β = Type II error = 0.20 (power = $1 - \beta$ = 0.80) were applied.

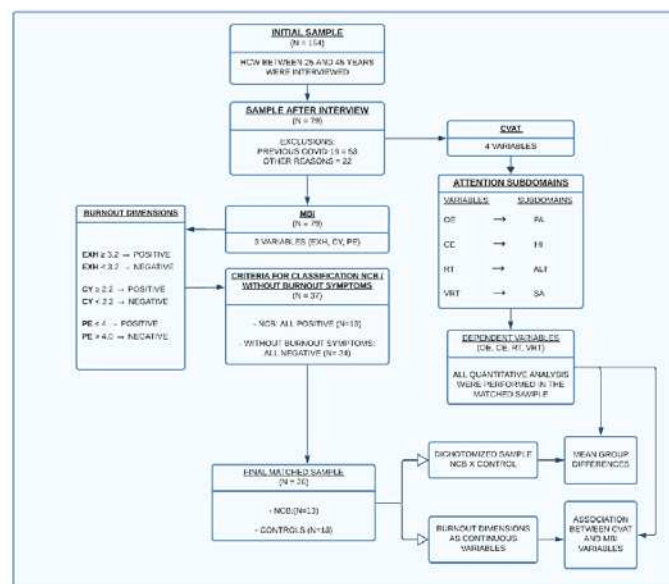


Figure 1. Flowchart explaining the study design. Abbreviations: CVAT, Computerized Visual Attention Test; MBI, Maslach Burnout Inventory; OE, omission errors; FA, focused attention; CE, commission errors; HI, hyperactivity/impulsivity factor; RT, reaction time; ALT, alertness; VRT, intraindividual reaction time variability; SA, sustained attention; EX = mean exhaustion; CY, mean cynicism; PE, mean personal efficacy; HCW, healthcare workers; NCB, non-clinical burnout.

When the participants were dichotomized according to the presence or absence of burnout symptoms, we performed MANCOVAs because they would account for any potential correlations between the dependent variables (attention subdomains). Thus, hypothetically, the MANCOVAs could show significant differences between the means while the individual ANCOVAs and the *t*-tests did not. However, irrespective of the results of the MANCOVAs, we always performed post hoc *t*-tests to determine where significant group differences in attention performance existed. As all the post hoc comparisons are variations of *t*-tests, we performed power analyses considering independent *t*-tests. We estimated the minimum differences (Δ) considering that they must reach magnitude levels that have clinical significance. For each variable of the abbreviated attention test (version 1.5 min), the population standard deviation and the mean difference with a real clinical significance were estimated based on comparisons (larger samples in previous studies) between healthy controls and patients with clinically defined attention disorders. In addition, some previous investigators define objective cognitive impairment in a particular domain as a score that is 1.5 standard deviations (SD) or more below the normative mean [56]. Considering all these matters, we performed a power analysis with the lowest Cohen's *d* among the four CVAT variables. For an allocation ratio of 1 and differences of 1.5 SD above the normative mean (note that in the CVAT, a higher score means a poorer performance), we found that the minimum sample size was 18 subjects, 9 in each group. Therefore, considering $\alpha = 0.05$, $\beta = 0.20$, power = 0.80, and $d = 1.5$ the present study reached an adequate sample size for the analysis of any possible mean differences in attentional performance between the two groups ($n = 26$, 13 in each group).

When burnout was characterized as a continuous variable, the relationships between each one of the three burnout dimensions with the variables of the CVAT (attention subdomains) were analyzed using Pearson correlation coefficients (*R*). In regression research, the most common effect size is the squared Pearson correlation, R^2 . Effect size is used to decide a priori what relationship should be considered for practical significance. Consequently, the first task in a sample size analysis for correlation analysis should be the identification of the magnitude of the correlation expected in the population. Unfortunately, in the present study, we had no empirical basis for any presumed population correlation (ρ). When no other rationale is available, [57] recommended that $R^2 = 0.25$ should serve as an upper limit. Additionally, Cohen [58] suggested that $R^2 = 0.26$ is a large regression effect. As a last resort, we here considered ρ between 0.50 and 0.55. Using these large-size effects, the minimum sample size varied between 29 and 23 subjects, respectively. Thus, our sample size ($n = 26$) was within this range.

2.4. Procedures

We provided a comprehensive description of all elements involved in this study, following the guidelines proposed by the ©STROBE initiative [59]. After applying exclusion and inclusion criteria (interview), the selected participants filled out the MBI. Then, participants were divided into two groups based on their scores across the inventory's three dimensions: controls and those exhibiting significant burnout symptoms, the latter group hereafter referred to as the non-clinical burnout (NCB) group. Finally, they performed the continuous visual attention test (CVAT). The researchers who administered the CVAT were blinded to the participants' burnout symptoms. All quantitative analyses were performed using the matched groups.

The CVAT assessed four distinct attention subdomains, while the Maslach inventory measured three different burnout dimensions. We analyzed the mean group differences in attention performance, considering the dichotomized sample (controls vs. NCB). Additionally, within the selected sample, we treated the burnout dimensions as three continuous variables and examined any significant relationships between the scores for each burnout dimension and the performance on the attention subdomains.

2.4.1. Computerized Visual Attention Test (CVAT)

The CVAT (Figure 2) involved a continuous stream of visual stimuli appearing on a computer screen at fixed intervals. Participants were instructed to press the spacebar as swiftly as possible when a specific target stimulus appeared, while refraining from responding to non-target stimuli. The test was self-paced, with stimuli presented for 250 ms and a 750-ms interstimulus interval. Out of 90 trials, 72 (80%) were targets, and 18 (20%) were non-targets. The test provided measures of reaction time (RT) and accuracy for both target and non-target stimuli, as well as a measure of response variability which offered insights into the stability of attentional performance and is linked to sustained attention [60].



Figure 2. Schematic overview of the CVAT showing the target (star) and non-target (diamond). The CVAT begins with on-screen instructions (A): “In this test, the computer alternately displays the indicated figures in the center of the screen. You must press the spacebar using your dominant hand as fast as you can whenever the star appears in the center of the screen. If the other figure appears, you should not press the space bar”. Both the target (B) and the non-target (C) remained on the screen for 250 milliseconds (ms). The test consists of 90 trials, with either of the two figures presented in each trial. The interstimulus interval is 1 s, resulting in a total test duration of 1.5 min. Key variables include Omission Errors (OE), Commission Errors (CE), average Reaction Time of correct responses (RT), and Intraindividual Variability of Reaction Time (VRT, standard deviation of the RTs during the test). The CVAT [46] is available for research and clinical use by licensed psychologists. Requests for access can be made to the corresponding author Prof. Sergio L. Schmidt. There are versions in English, Spanish, and Portuguese. CVAT: Continuous Visual Attention Test.

The average reaction time for correct responses (RT) was calculated for each participant. Furthermore, intraindividual reaction time variability (VRT) for all correct responses to the target was determined, estimated by the standard deviation (SD) of all correct RTs per individual. Accuracy was determined by tallying the number of omission and commission errors (OE and CE, respectively). An omission error was counted when a participant failed to respond to a target, while a commission error represented any incorrect responses to non-target stimuli.

2.4.2. Maslach Burnout Inventory (MBI)

The MBI [61] is a self-report questionnaire that took approximately 10 to 15 min to complete and comprised 16 items assessing the three most important symptoms of burnout: exhaustion (sample item: ‘I feel used up at the end of the work-day’), cynicism (sample item: ‘I have become less enthusiastic about my work’), and reduced personal efficacy (sample item: ‘In my opinion, I am good at my job’). Participants indicated their frequency of experiencing each item on a 7-point scale, which ranged from “never” to “every day.” Scores for each dimension were derived by summing the scores for the respective items and then determining the average score.

2.5. Statistical Analysis

2.5.1. Mean Differences in Attention Performance between Two Groups Dichotomized According to the Presence of Burnout Symptoms

To verify whether there were significant differences between HCWs with high burnout symptoms and those without burnout symptoms, a MANCOVA was performed including RT, VRT, OE, and CE as dependent variables, and the group (high non-clinical burnout vs. no burnout) as the independent variable. Box's M-test was used to assess the homogeneity of the covariance matrices. A significant MANCOVA indicates that at least one dependent variable is different between the groups, thus allowing for further post hoc univariate ANCOVAs. A MANCOVA/ANCOVA approach was chosen as it has been shown to give robust results even when variables are not normally distributed [62]. To determine whether there were mean differences between the two groups, we also performed independent *t*-tests on the CVAT variables.

In the present study, we balanced the groups considering potential confounders (age and sex). As we have a matching design, it was possible to perform the MANCOVA and respective ANCOVAs without confounders and covariates. However, matching is more complex than just balancing groups for potential confounders. Covariates and confounders are typically included in statistical models to account for the variance they explain in the dependent variables. Some investigators [63] have proposed that the benefit obtained from accounting for the variance that the confounders explain in the dependent variables is greater than the increase of power obtained without confounders. Therefore, even in a matched design sometimes it is necessary to control for the matching factors in the analysis. For this reason, we decided to perform MANCOVAs and ANCOVAs with and without confounders. Age and sex were used as covariates. We also performed the MANCOVAs and respective ANCONVAs considering OE, CE, and VRT as dependent variables and RT, age, and sex as confounders. The use of RT as a cofactor was proposed by Linden et al. [7]. These authors considered that CEs are inversely related to RTs and, thus, average RT might obscure differences in CE and VRT.

It should be mentioned that fatigue was not considered as a confounding variable for two reasons: first, we did not include shift workers and second, the CVAT lasts only 1.5 min.

2.5.2. Correlation between Burnout Dimensions and Attention Subdomains

All of the possible associations between the three burnout variables and the CVAT variables were analyzed with Pearson correlation coefficients. Here, we checked whether the data satisfied all of the necessary assumptions of correlation linear analysis. The following assumptions were carefully analyzed: linearity (relationships of the predictors to the outcomes should be linear), normality of the errors (the residuals should be normally distributed), homoscedasticity (the variance of the residuals should be homogeneous across levels of the predicted values), and independence (the errors associated with one observation should not be correlated with the errors of any other observation). Furthermore, we also verified if any single observation or small group of observations made significant differences in the correlation coefficients (outliers and influential observations).

3. Results

One hundred and fifty-four HCWs were interviewed; 53 were excluded because of a previous COVID-19 infection and 22 for other medical reasons. From the remaining 79 subjects, 13 could be classified into the NCB group and 24 did not show any relevant symptom in all three burnout dimensions. The controls were matched with the 13 NCB subjects based on age, sex, and HCW category. After applying the matching criteria, 13 eligible participants without burnout symptoms were selected to be compared with 13 NCB subjects.

For the final selected sample ($n = 26$), the age ranged from 25 to 44 years (mean = 35.31; standard deviation = 5.47), with 17 men and 9 women. The sample of health professionals

consisted of 11 physicians and 15 nursing professionals. Table 1 presents demographic data and MBI results. Although the two groups were not perfectly matched, we did not find any significant group differences in the demographic data. Regarding MBI scores, because of the definition of the NCB group, significant group differences (NCB vs. controls) were found for the three burnout dimensions.

Table 1. Demographics and MBI data ($n = 26$).

Demographics and Burnout Dimensions	Non-Clinical Burnout ($n = 13$)	Controls ($n = 13$)	Group DIFF (P)
FEMALE	5 (38.46%)	4 (30.76%)	ns
AGE	34.23 $\pm$ 7.0	36.38 $\pm$ 3.2	ns
PHYSICIANS	5 (38.46%)	6 (46.15%)	ns
NURSES AND NURSE AIDES	8 (61.15%)	7 (53.38%)	ns
AVERAGE EXH	5.11 $\pm$ 0.59	0.73 $\pm$ 0.43	<0.01
AVERAGE CY	4.49 $\pm$ 1.12	0.14 $\pm$ 0.25	<0.01
AVERAGE PE	3.23 $\pm$ 0.32	5.53 $\pm$ 0.56	<0.01

Each continuous variable is expressed as the mean $\pm$ standard deviation. Abbreviations: EXH, Exhaustion; CY, Cynicism; PE, Personal Efficacy; ns (non-significant); P, proof value. Significant group differences are indicated in BOLD.

Figure 3 presents the raw data of the four CVAT variables according to the two dichotomized groups. Visual inspection indicated that CE is higher in the NCB group as compared to controls. Average reaction time tended to be higher in controls, but the amplitude of the difference is within the range of one standard error of the mean.

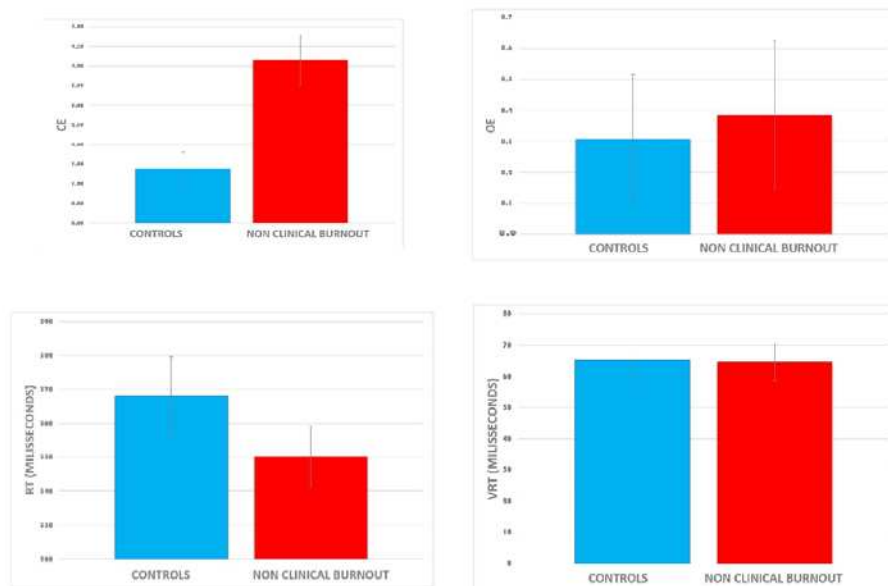


Figure 3. Means of each CVAT variable according to the group (raw data). Data are expressed as the mean $\pm$ standard error of the mean. Abbreviations: CE, commission errors; OE, omission errors; RT, reaction time; VRT, intraindividual reaction time variability. Group differences reached significance for the CE variable.

The MANCOVA showed a significant overall effect of non-clinical burnout on the attention test, $F(4, 21) = 3.55$, $p = 0.023$, $\eta^2 = 0.40$. After adjusting for covariates (age, sex,

and RT), similar results were found. The univariate ANCOVAs showed that non-clinical burnout affected CE, $F(4, 21) = 12.90$, $p = 0.001$, $\eta^2 = 0.35$, but not VRT [$F(4, 21) = 0.003$, $p = 0.956$], OE [$F(4, 21) = 0.06$, $p = 0.811$], or RT [$F(4, 21) = 1.23$, $p = 0.279$]. Analysis of covariance of VRT controlled for RTs, revealed a tendency for a significant group difference showing that, compared to the controls, the NCB group had higher VRT ($p = 0.07$, two tailed).

Considering CE as the dependent variable, Pearson correlation coefficients (R) reached statistical significance for the three burnout dimensions (Table 2): exhaustion ($R = 0.545$, $p = 0.004$); cynicism ($R = 0.563$, $p = 0.003$), and reduced personal effectiveness ($R = -0.522$, $p = 0.006$). It should be mentioned that we investigated all linear regression assumptions (plots of residuals against predicted values, histograms of residuals, and tests of normality) as well as Cook's distances, DFBETAs, and Mahalanobis distances).

Table 2. Pearson correlation coefficients ($n = 26$).

Variables	Average EXH	Average CY	Average PE
CE			
R Pearson	0.545 *	0.563 *	−0.522 *
<i>p</i> -value	0.004	0.003	0.006
OE			
R Pearson	0.013	0.047	−0.079
<i>p</i> -value	0.950	0.818	0.703
RT			
R Pearson	−0.228	−0.318	0.334
<i>p</i> -value	0.262	0.114	0.095
VRT			
R Pearson	0.011	−0.106	0.074
<i>p</i> -value	0.957	0.608	0.720

The table includes correlation coefficients (R Pearson) and *p*-values for variables CE, OE, RT, and VRT against averages of EXH, CY, and PE. "R Pearson" refers to the Pearson correlation coefficient, which measures the strength and direction of the relationship between two variables. "*p*-value" refers to proof value. * Indicates that the result is significant at $p < 0.01$. Abbreviations: EXH, Exhaustion; CY, Cynicism; PE, Personal Efficacy; CE, commission errors; OE, omission errors; RT, reaction time; VRT, intraindividual reaction time variability.

4. Discussion

Our data indicated that specific attention deficits occur in employees who are still on the job but experience burnout symptoms (non-clinical burnout). The performance on the attention test suggests that the behavior of the NCB participants tended to be guided by more impulsive responses than controls.

4.1. Executive Deficits in NCB in Healthcare Workers during the COVID-19 Pandemic

This study investigated NCB and attention performance deficits among healthcare workers during the COVID-19 pandemic, a context not extensively explored in existing literature. The pandemic's unprecedented stressors provided a unique opportunity to study NCB in an intensified setting. Accordingly, in this study, the sample of NCB subjects manifested significant levels of exhaustion and depersonalization and a reduced sense of personal or professional accomplishments. In the context of our study, healthcare workers during the COVID-19 pandemic faced significant challenges in preserving their resources, such as emotional and physical energy, due to high stress, resource constraints, and increased workload. This depletion of resources might lead to decreased self-regulation, manifesting as increased impulsivity or hyperactivity in attention tasks.

The basic paradigm of the CVAT task is characterized by a serial presentation of target and non-target stimuli, and the subject's task is to respond to target stimuli and control inadequate responses [37–41]. Inhibition is the ability to control inadequate responses, measured by the number of CEs. The finding of a higher number of CEs suggests that NCB individuals may have difficulties with attention in daily tasks.

The significant difference between controls and NCB individuals in the impulsivity-hyperactive subdomain may indicate that these individuals are more prone to make mistakes during their working time. In this regard, it is acknowledged that sustained attention and response inhibition are aspects of executive control [64]. Executive control is a term that refers to a set of cognitive processes underlying voluntary regulation of perception and motor responses, to adaptively deal with changing task demands [65]. Individuals whose executive control is impaired typically show deficits in their ability to inhibit inappropriate motor responses [31]. Therefore, our data corroborates the hypothesis of executive dysfunction in the NCB individuals. However, the ability to sustain attention is also part of executive control. In this regard, it would be expected that NCB subjects would be impaired in the VRT variable. However, contrary to this expectation, VRT was not affected.

The absence of any significant difference in the VRT variable may be explained by the associations among VRT, RT, and CE. As indicated by the raw data (Figure 3), the average VRT did not differ between controls and NCB subjects. In contrast, NCB subjects tended to be faster than controls. However, there was a negative correlation between reaction time and inhibition errors. Analysis of covariance, in which we controlled for RTs, confirmed a significant effect for Group. Post-hoc ANCOVAs (group comparisons, controlling for RT) showed a significant group difference in CE and a tendency for significance in VRT. This tendency reflected that the VRT was higher in NCB subjects as compared to controls. In addition, previous studies [66] have demonstrated that VRT can be adequately measured using short-duration tests (e.g., 1-min test) provided that these tests have several measured reaction times, usually more than 25 trials. As the CVAT has 90 trials (72 correct targets) and lasts more than 1 min, the present finding of a higher VRT in NCB workers when the data were controlled for RTs corroborates our hypothesis of an executive attention problem in this population.

Our findings support earlier clinical observations reporting that clinical burned-out individuals have difficulties with attention in daily tasks [2,7]. Linden et al. [7] administered the Sustained Attention Response Test (SART) and demonstrated that participants with clinical burnout performed significantly worse on CE and VRT. However, in an apparent contradiction to our finding, this study also reported that NCB and controls did not differ in SART performance. It should be mentioned that the SART has only 11% of non-targets whereas the CVAT has 20%. An increased number of non-targets in the CVAT increases the probability of identifying subjects who made incorrect responses due to impulsivity. Thus, it is possible that the CVAT would be more accurate than the SART to evaluate inhibition responses. In addition, it should be mentioned that Linden et al. [7] also reported that the level of executive attention deficits was highest in the clinical burnout group, intermediate in the high (non-clinical) burnout employees, and lowest in the control group.

To our knowledge, the current study is the first to describe empirical findings indicating that non-clinical burnout is associated with deficits in executive control. Recently, Koutsimani and Montgomery [27] reported visuospatial deficits in NCB subjects. Considering the pivotal role of attention in cognition, we speculate that these visual spatial deficits may, at least in part, reflect executive attention deficits.

4.2. Limitations

Although the current study describes important inhibitory deficits in NCB, there were also some limitations.

First, the sample size was small, which limits the generalizability of the results and makes the statistical differences more susceptible to Type I error. However, the finding of a significant difference in CE with small groups suggests that the effects sizes of cognitive deficits associated with burnout may be substantial.

Secondly, burnout was examined through self-reported questionnaires, thus participants' answers could be affected by potential self-report biases. Future studies should also be conducted using structured clinical interviews.

Thirdly, we used only one test that measures one cognitive domain. Although the subject's ability to attend to specific stimulus and inhibit inadequate responses (attention) must be established before the most complex functions are evaluated, future studies with larger sample sizes and using tests that assess other cognitive domains (memory, language, etc.) will allow a better comprehension of the influence of NCB in cognition.

Finally, we did not control for the subjects' stress levels, resources, self-regulation, and workload in this study. Although this is a cross-sectional study and does not allow any inference regarding causal effects, controlling the variables mentioned above would be helpful to investigate whether depletion of resources might lead to decreased self-regulation, manifesting as increased impulsivity or hyperactivity in attention tasks.

5. Conclusions

We showed that HCWs with high burnout levels who are still on the job performed badly on variables that are linked to specific attention subdomains (sustained attention and impulsivity). Our study suggests a way to objectively assess attentional impairments associated with burnout symptoms by using a brief computerized attention test alongside a self-reported burnout questionnaire. The current study provides evidence that using the CVAT with a self-reported burnout questionnaire could be used to identify individuals with high burnout symptoms and executive attention deficits. Adding this objective tool (CVAT) could help to develop new strategies to reduce accidents related to burnout at work, especially in cases mostly affected by impulsivity. Moreover, it would help policymakers measure burnout's actual impact on working populations, particularly in countries with a high burnout prevalence, such as Brazil [67].

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APÊNDICE D - Artigo publicado “*Effect of exposure to Covid-19 patients on attention performance in workers at Gaffrée and Guinle University Hospital*”

Cad Bras Med COVID-19 (Especial): 1-36, 2020

Efeito da Exposição a Pacientes com Covid-19 no Desempenho Atencional em Funcionários do Hospital Universitário Gaffrée e Guinle

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RESUMO

Objetivo: Investigar se a exposição a pacientes com COVID-19 poderia alterar o desempenho atencional de funcionários do Hospital Universitário Gaffrée & Guinle. **Método:** Um teste computadorizado de atenção visual foi aplicado em 161 funcionários. Após os critérios de exclusão (uso de medicação psicotrópica), 124 funcionários foram divididos em 2 grupos: Baixa ou nenhuma exposição semanal e alta exposição semanal a pacientes com COVID-19. **Resultados:** O grupo com alta exposição apresentou piora significativa na atenção sustentada ($p < 5\%$). **Conclusão:** O pior desempenho na atenção sustentada pode refletir lapsos atencionais, o que poderia aumentar o risco de acidentes de trabalho no grupo de funcionários que trabalham diretamente com pacientes infectados pelo SARS-CoV-2.

Palavras-chave: atenção, variabilidade do tempo de reação, COVID-19.

Effect of Exposure to Covid-19 Patients on Attention Performance in Workers at Gaffrée and Guinle University Hospital

ABSTRACT

Objective: To verify if attention performance was affected by exposure to COVID-19 patients in workers at Gaffrée e Guinle University Hospital. **Method:** A computerized visual attention test was applied to 161 employees. After exclusion criteria (use of psychotropic medication), 124 workers were dichotomized into 2 groups: Low or no weekly exposure ($n = 44$) and high weekly exposure to patients with COVID-19 ($n = 80$). **Results:** The group with high exposure had poorer attention performance ($p < 5\%$). **Conclusion:** The lower performance reflected attentional lapses, which may increase accident risk at work in the group of workers exposed to patients with COVID-19.

Keywords: attention, variability of reaction time, COVID-19.

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INTRODUCTION

During the current COVID-19 pandemic, workers in close contact with COVID-19 patients are particularly vulnerable to psychological stress¹. Previous studies have suggested that individual brain network under acute stress controls the cognitive consequences of threat². Stress responses via catecholaminergic pathways may have selective effects on brain regions that include the temporoparietal and cingulate cortices, amygdala, thalamus, striatum, and the brainstem. Changes in these regions are followed by changes in the executive control network in the prefrontal cortex. These regions are associated with attention performance³. Accordingly, Schmidt et al.⁴ reported deficits in attention performance under stress. Therefore, attentional impairments would be expected in workers in close contact with COVID-19 patients. However, as far as we know, this issue has not been studied during the current pandemic.

Attentional performance can be measured using computerized Go/No-go reaction-time paradigms⁵. In Brazil, the Computerized Visual Attention Test (CVAT) is validated for clinical use⁶. Schmidt et al.⁷, using positron emission tomography, showed that the CVAT activates the prefrontal cortex. Considering the possible effect of stress on the prefrontal cortex, attention deficits would be expected in workers in contact with COVID-19 patients.

Here we aimed to investigate if hospital employees with high exposure to COVID-19 patients showed attentional impairments as compared to those with low exposure.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the Gaffrée and Guinle University Hospital (Plataforma Brasil CAAE:30547720.3.0000.0008) and was in accordance with the Declaration of Helsinki for medical research involving human subjects. Written informed consent was obtained from all the participants.

Participants

All participants were workers at the University Hospital. Age ranged between 22 to 66 years. Exclusion criteria: Diabetes mellitus; current or previous neurologic disease; and use of drugs

that can impair attention, like hypnotic sedative drugs, tricyclic antidepressants, anti-psychotics, muscle relaxants, antihistamines, and glucocorticoids.

Groups were divided accordingly to COVID-19 weekly hours of exposure (< 24 hours, low-exposure; ≥ 24 hours, high-exposure).

CVAT

Participants were seated in front of a laptop computer to allow the dominant hand to be placed over the keyboard. Before each task, the examiner instructed the subject to press the spacebar as fast as possible each time a specific visual target stimulus was displayed on the monitor. The test started with instructions and a practice session. The full version of the CVAT lasts 15 minutes^{5,8,9,10}. However, as the present investigation was designed to assess a large number of participants in a short time period, we administered an abridged form of the CVAT (90 seconds). This form had previously been used in elderly^{11,12}. It includes 90 trials (80% targets, 20% non-target) with an interstimulus interval of 1 second. The types of measures included omission errors, commission errors, reaction time, and intraindividual variability of reaction times. Participants with less than 50% of correct responses on CVAT were excluded. Response times lower than 150 milliseconds were excluded.

STATISTICAL ANALYSIS

A MANCOVA was performed including all the CVAT variables as dependent variables and exposure to COVID-19 as independent variable (low vs. high exposure). Age and sex were cofactors. In case of a significant overall MANCOVA, post-hoc ANCOVAs of each dependent variable was checked for statistical significance. Significance was set at $p < 5\%$. Analyses were performed using SPSS 25.

RESULTS

The continuous visual attention test (CVAT) was administered in 161 hospital workers. After applying the exclusion criteria, 124 workers were included in this study. There was not significant group difference in mean ages (high-exposure, $n=80$, Mean= 42.71 years, Standard deviation=10.02 years; low-exposure, $n=44$, Mean= 39.61 years, Standard deviation=10.68 years).

The percentage of females did not differ (High-exposure=66%; Low-exposure=65%).

Analysis of the raw data showed that the

high-exposure group made more errors, had slower response time, and higher variability of reaction time (Table1).

Table 1. Raw scores (CVAT)

	Low Exposure (n= 44)	High Exposure (n = 80)
CVAT Variables	1.77 ± 4.67	3.54 ± 7.40
Omission Errors	14.77 ± 13.55	18.61 ± 13.44
Commission Errors	370.73 ± 36.05	388.26 ± 47.28
Reaction Time (ms)	65.32 ± 17.43	81.20 ± 35.25
Variability of Reaction Times (ms)*	1.60 (0-10)	1.29 (0-21)

Abbreviation: CVAT= Computerized Visual Attention Test. CVAT variables are represented by mean ± standard error of the mean. * represents group differences that reached significant level < 5%.

The overall MANCOVA, after correction for age and sex, was statistically significant ($F=2.72$, $df=4/117$, $P=0.03$). Sex and age also reached significance. Further analysis using post-hoc ANCOVAs showed that the mean intraindividual variability of reaction times of the correct responses was significantly higher in the high exposure group as compared to their counterparts with low exposure to COVID-19 patients ($F=6.68$, $df=1/120$, $P=0.01$). Conversely, group differences in reaction time, omission and commission errors did not reach a significant difference.

DISCUSSION

Hospital employees with a close contact with COVID-19 patients performed worse in the CVAT, particularly in the variability of reaction time. This variable is associated with sustained-attention⁸. Schmidt et al.⁴ have described that sustained-attention subdomain can be affected by a stressful situation. One explanation for this phenomenon could be an increased stimulation for the adrenal production of glucocorticoids in stressful situations by the hypothalamic-pituitary axis^{14,15}. These glucocorticoids bind into receptors located in the prefrontal cortex¹⁴, a cerebral region

that plays a central role in sustained attention control, impairing attentional functioning.

The worse performance in the sustained attention subdomain may reflect lapses in attention¹⁶. Thus, the group with a higher COVID-19 patient exposition may be at a higher risk of work accidents, including SARS-CoV-2 contamination.

Limitations of this study included unequal sample sizes and the possible influence of other confounding variables, such as, sleep quality and previous COVID-19 infection. As age and sex affected CVAT, further investigation should address this question using samples paired by age and sex including sleep quality and previous COVID-19 infection as covariates. Another limitation is the duration of the test. Although the test allowed 36 to 72 measurements of correct reaction times per participant, the short duration of the CVAT abridged version (90 seconds) may cause a reduction in the total number of errors, as compared to the 15-min version of the test. Thus, it would be of interest to assess performance with the longer CVAT form.

In conclusion, the present data support that hospital workers who are in close contact with COVID-19 patients show lapses of attention.

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APÊNDICE E - Ficha de coleta de dados da pesquisa



UNIVERSIDADE FEDERAL DO ESTADO DO RIO DE JANEIRO
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM NEUROLOGIA
HOSPITAL UNIVERSITÁRIO GAFFRÉE E GUINLE

Entrevistador: _____ Código do questionário: _____

Nome: _____

Idade: _____ Prontuário: _____

Peso: _____ Altura: _____ IMC: _____

Sexo: ☐ Masculino ☐ Feminino

TCLE preenchido: ☐ Sim ☐ Não

I. Critérios de Inclusão / Exclusão

1. Tabagismo: ☐ Sim ☐ Não 2. Alcoolismo: ☐ Sim ☐ Não

2. Estratificação do risco cirúrgico - Classificação ASA: ☐ I ☐ II ☐ III ☐ IV

3. Medicações em uso contínuo, ou recente:

Y corticóide ☐ antipsicótico ☐ opióide ☐ zolpiden ☐ antidepressivo tricíclico ☐ pré-gabanina

Y benzodiazepínico ☐ mirtazapina ☐ donaren ☐ trazodona ☐ antiepiléptico ☐ eszopiclona

Y drogas ilícitas em geral. Se sim, qual(is): _____ ☐ nenhuma das anteriores

4. História cirúrgica prévia:

Y cirurgia neurológica ☐ cirurgia cardíaca ☐ cirurgia de urgência ☐ anestesia geral há até 1 ano

Y complicação cirúrgica no intraoperatório ☐ nenhuma das anteriores

5. Presença de doença neurológica ou psiquiátrica que afetem a cognição: ☐ Sim ☐ Não

6. Presença de comorbidades: ☐ Sim ☐ Não Se sim, qual(is): _____

7. Cirurgia a ser realizada: ☐ colecistectomia videolaposcópica ☐ tireoidectomia

Y Outra: _____

II. Identificação

1. Data de nascimento: ____/____/____

2. Endereço: _____

3. Bairro: _____ 4. CEP: _____

5. Cidade: _____ 6. Telefone(s): _____

7. Escolaridade: _____ 8. Profissão anterior/atual: _____

9. Medicações em uso: ☐ Sim ☐ Não Se sim, qual(is): _____

10. Número de horas de sono na noite anterior: _____

UNIVERSIDADE FEDERAL DO ESTADO DO RIO DE JANEIRO – UNIRIO
 HOSPITAL UNIVERSITÁRIO GAFFRÉE E GUINLE – HUGG
 GERÊNCIA DE ENSINO E PESQUISA E COMITÊ DE ÉTICA E PESQUISA
Termo de Consentimento Livre e Esclarecido – TCLE

Convidamos o(a) Senhor(a) a participar do projeto de pesquisa ALTERAÇÕES COGNITIVAS RELACIONADAS A TÉCNICA ANESTÉSICA, sob a responsabilidade da pesquisadora CAROLINA RIBEIRO MELLO. O projeto consiste na realização da avaliação da cognição no pós-operatório, que consiste na avaliação da capacidade de memória, de manter atenção e concentração, de leitura e fala com clareza. O estudo compara duas técnicas anestésicas diferentes (anestesia geral venosa e anestesia geral inalatória), ambas já muito bem estabelecidas na literatura, de uso comum e rotineiro no nosso Hospital, você será sorteado para ser incluído ao acaso em um grupo. Para tal, será necessária uma avaliação pré-operatória, onde teremos um parâmetro comparativo prévio, e no período após a cirurgia em 3 momentos diferentes: no dia seguinte, 7 e 30 dias após, a mesma. A proposta surgiu de estudos anteriores que sugerem uma ação protetora anti-inflamatório do cérebro relacionada ao uso de uma das mediações usualmente utilizadas.

O objetivo desta pesquisa é avaliar possíveis alterações na cognição, incluindo avaliação de atenção e memória relacionadas a diferentes técnicas anestésicas, ambas usuais já utilizadas em nossa rotina clínica. A intenção é avaliar se nossos anestésicos têm alguma ação protetora na inflamação do cérebro. E a partir de então estimular a utilização de determinado agente anestésico, ou não.

O(a) senhor(a) receberá todos os esclarecimentos necessários antes e no decorrer da pesquisa e lhe asseguramos que seu nome não aparecerá sendo mantido o mais rigoroso sigilo pela omissão total de quaisquer informações que permitam identificá-lo(a).

A sua participação terá duração de 30 minutos, se dará por meio de realização de um teste computadorizado de 15 minutos de duração, que lhe será explicado minuciosamente durante a avaliação e um questionário de 3-5 minutos de duração, ambos serão realizados em 4 diferentes momentos: 1. Antes da cirurgia, 2. No dia seguinte ainda na enfermaria, 3. Na consulta de retorno de 1 semana e 4. Na consulta de retorno de 30 dias após a cirurgia no ambulatório de cirurgia, além da coleta de sangue em dois momentos diferentes: 1. No pré-operatório que será realizada no momento da punção venosa, já prevista, antes do procedimento, que será realizada ainda na enfermaria, sem nenhum acréscimo de desconforto ao senhor(a) e 2. No dia seguinte antes da alta, será realizada uma nova coleta de sangue, em outro local, com uma outra punção, como as realizadas em laboratório, para coleta de sangue. Os riscos relacionados à coleta de sangue são: hematoma no local, necessidade de múltiplas punções, e infecção local. O ato anestésico e cirúrgico transcorrerá normalmente, conforme as rotinas já estabelecidas no hospital.

Os riscos decorrentes de sua participação na pesquisa, são os mesmos decorrentes do procedimento cirúrgico o que o senhor(a) será submetido, uma vez que serão utilizadas duas técnicas anestésicas já bem estabelecidas na literatura, e não existe nenhuma interferência no procedimento cirúrgico, nosso estudo é observacional dos efeitos da anestesia avaliados pelo teste computadorizado, que traz nenhum risco adicional, sempre haverá algum risco de manipulação dos seus dados, e que serão diminuídos com a ocultação do seu nome. Se você aceitar participar, contribuirá para o meio científico, onde nos possibilitará aprofundarmos o entendimento da ação dos anestésicos utilizados na prática diária em nosso meio, e influenciará nas escolhas futuras do anestesista, tornando nossa atuação cada vez mais segura para a sociedade, e reduzindo o risco anestésico.

O(a) Senhor(a) pode se recusar a responder (ou participar de qualquer procedimento) qualquer questão que lhe traga constrangimento, podendo desistir de participar da pesquisa em qualquer momento sem nenhum prejuízo para o(a) senhor(a).



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Termo de Consentimento Livre e Esclarecido – TCLE

Não há despesas pessoais para o participante em qualquer fase do estudo, todas as suas avaliações serão feitas nos dias das suas consultas com seu cirurgião. O teste computadorizado de atenção ou nos exames laboratoriais a serem realizados, serão absorvidos pelo orçamento da pesquisa. Também não há compensação financeira relacionada a sua participação, que será voluntária.

Caso haja algum dano direto ou indireto decorrente de sua participação nessa pesquisa, você receberá assistência integral e gratuita, pelo tempo que for necessário, obedecendo os dispositivos legais vigentes no Brasil. Caso você/senhor/senhora sinta algum desconforto relacionado aos procedimentos adotados durante a pesquisa, o senhor(a) pode procurar o pesquisador responsável para que possamos ajudá-lo.

Os resultados da pesquisa serão divulgados no Hospital Universitário Gaffrée e Guinle/UNIRIO podendo ser publicados posteriormente. Os dados e materiais utilizados para esta pesquisa ficarão sob a guarda do pesquisador, podendo ser armazenados em formato digital, sendo preservados o anonimato e a indisponibilidade de qualquer informação que permita a sua identificação em qualquer pesquisa que os utilize.

Se o(a) Senhor(a) tiver qualquer dúvida em relação à pesquisa, por favor telefone para: Carolina Ribeiro Mello, no Hospital Universitário Gaffrée e Guinle, no telefone: 21 2264-4842 e 21 99635-5983, disponível inclusive para ligação a cobrar, e carolmello77@gmail.com.

Este projeto foi aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário Gaffrée e Guinle -UNIRIO/EBSERH. O CEP é composto por profissionais de diferentes áreas cuja função é defender os interesses dos participantes da pesquisa em sua integridade e dignidade e contribuir no desenvolvimento da pesquisa dentro de padrões éticos. As dúvidas com relação à assinatura do TCLE ou os direitos do participante da pesquisa podem ser esclarecidos pelos telefones (21) 2264-5177, whatsapp (21)97138-5971 ou e-mail cephugg@gmail.com, horário de atendimento das 08h:00 às 17h:00, de segunda a sexta-feira. O CEP-HUGG se localiza no quarto andar do HUGG, pavilhão hospitalar, acesso pela escada ou elevador ao final do corredor que leva à enfermaria de Ortopedia – Rua Mariz e Barros 775, Tijuca, Rio de Janeiro, RJ. CEP: 20270-004. Caso concorde em participar, pedimos que assine este documento que foi elaborado em duas vias, uma ficará com o pesquisador responsável e a outra com o Senhor(a).

Nome / assinatura

Carolina Ribeiro Mello

CREMERJ 52.67867-8

Rio de Janeiro, ____ de ____ de ____.

DATA: _____ D: 0

CÓDIGO

MINI EXAME DO ESTADO MENTAL (MEEM)

Instruções: as palavras em negrito devem ser lidas alto, clara e lentamente pelo examinador. Substituições aparecem entre parênteses. Circule o "0" se a resposta for incorreta ou o "1" se a resposta for correta.

ORIENTAÇÃO NO TEMPO	RESPOSTA	ESCORE
Em que ano nós estamos?		0 1
Em que estação do ano nós estamos?		0 1
Em que mês nós estamos?		0 1
Em que dia do mês nós estamos?		0 1
ORIENTAÇÃO NO ESPAÇO		
Onde nós estamos agora?		0 1
Em que estado nós estamos?		0 1
Em que cidade nós estamos?		0 1
Em que bairro nós estamos? (parte da cidade ou rua próxima)		0 1
O que é este prédio em que estamos? (nome, tipo ou função)		0 1
Em que andar estamos?		0 1
REGISTRO		
Agora preste atenção. Eu vou dizer três palavras e o (a) Sr.(a) vai repeti-las quando eu terminar. Memorize-as, pois eu vou perguntar por elas novamente, dentro de alguns minutos. Certo? As palavras são: REAL [pausa], MALA [pausa], CASA [pausa]. Agora repita as palavras para mim. [Permita 5 tentativas, mas pontue apenas a primeira]		
REAL		0 1
MALA		0 1
CASA		0 1
ATENÇÃO E CÁLCULO [Série de 7]		
Agora eu gostaria que o (a) Sr.(a) subtraísse 7 de 100 e do resultado subtraísse 7. Então continua subtraindo 7 de cada resposta até eu mandar parar. Entendeu? [pausa] Vamos começar: quanto é 100 menos 7? Dê um ponto para cada acerto. Se não atingir o escore máximo, peça: Soletre a palavra MUNDO. Corrija os erros de soletração e então peça: Agora soletre a palavra MUNDO de trás para frente (O-D-N-U-M). [Dê 1 ponto para cada letra na posição correta. Considere o maior resultado.]	{93} _____ 0 1 {86} _____ 0 1 {79} _____ 0 1 {72} _____ 0 1 {65} _____ 0 1	
	Soma do cálculo	_____
	ODNUM	_____
	Soma do Mundo	_____
MEMÓRIA DE EVOCÇÃO		
Peça: quais são as 3 palavras eu pedi que o Sr.(a) memorizasse? [Não forneça pistas]		
REAL		0 1
MALA		0 1
CASA		0 1
LINGUAGEM		
[Aponte o lápis e o relógio e pergunte:]		
O que é isto? (lápis)	_____	0 1
O que é isto? (relógio)	_____	0 1
Agora eu vou pedir para o Sr.(a) repetir o que eu vou dizer, certo? Então repita: "NEM AQUI, NEM ALI, NEM LÁ".		0 1

DATA: _____ D: 0

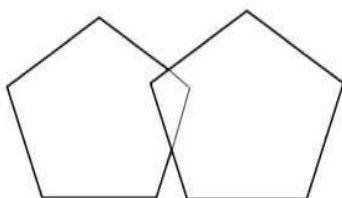
CÓDIGO

Agora ouça com atenção porque eu vou pedir para o Sr.(a) fazer uma tarefa. [pausa] Preste atenção, pois eu só vou falar uma vez. [pausa] Pegue este papel com a mão direita [pausa], com as duas mãos dobre-o ao meio uma vez [pausa] e em seguida jogue-o no chão.		
Pegar com a mão direita	_____	0 1
Dobrar ao meio	_____	0 1
Jogar no chão	_____	0 1
Por favor, leia isto e faça o que está escrito no papel. Mostre ao examinado a folha com o comando: FECHE OS OLHOS		0 1
Peça: por favor, escreva uma sentença. Se o paciente não responder, peça: escreva sobre o tempo. [Coloque na frente do paciente um pedaço de papel em branco e lápis ou caneta.]		0 1
Peça: por favor, copie este desenho. [Apresente a folha com os pentágonos que se interseccionam.]		0 1
TOTAL		
Pontos de corte: analfabetos: 18, 19; anos de estudo ≥ 1 : 23, 24		

FRASE

Frase: _____

PENTÁGONO



DATA: _____ D: 0

CÓDIGO

GAD-7

Durante as 2 últimas semanas, com que frequência você se sentiu incomodado por qualquer um dos problemas abaixo?

Problemas	Nenhuma vez	Alguns dias	Mais da metade dos dias	Quase todos os dias
Sentiu-se nervoso, ansioso ou muito tenso	0	1	2	3
Não foi capaz de impedir ou controlar as preocupações	0	1	2	3
Preocupou-se muito com diversas coisas	0	1	2	3
Sentiu dificuldade para relaxar	0	1	2	3
Ficou tão agitado que se tornou difícil permanecer sentado	0	1	2	3
Ficou facilmente aborrecido ou irritado	0	1	2	3
Sentiu medo com se algo horrível fosse acontecer	0	1	2	3

Resultado: _____

(resultado ≥ 10 considera-se indicador positivo para sinais e sintomas de transtornos de ansiedade)

DATA: _____ D: 0

CÓDIGO

ESCALA DE BEM-ESTAR ESPIRITUAL (FACIT_Sp-12)

Por favor, faça um **círculo** em torno do número que melhor corresponda ao seu estado durante os **últimos 7 dias**.

	PREOCUPAÇÕES ADICIONAIS	Nem um pouco	Um pouco	Mais ou menos	Muito	Muitis- simo
Sp 1	Sinto-me em paz	1	2	3	4	5
Sp 2	Tenho uma razão para viver	1	2	3	4	5
Sp 3	A minha vida tem sido produtiva	1	2	3	4	5
Sp 4	Custa-me sentir paz de espírito	1	2	3	4	5
Sp 5	Sinto que a minha vida tem um propósito	1	2	3	4	5
Sp 6	Sou capaz de encontrar conforto dentro de mim mesmo	1	2	3	4	5
Sp 7	Sinto-me em harmonia comigo mesmo	1	2	3	4	5
Sp 8	Falta sentido e propósito na minha vida	1	2	3	4	5
Sp 9	Encontro conforto na minha fé ou crenças espirituais	1	2	3	4	5
Sp 10	A minha fé ou crenças espirituais dão-me força	1	2	3	4	5
Sp 11	A minha doença tem fortalecido a minha fé ou crenças espirituais	1	2	3	4	5
Sp 12	Independente do que acontecer com a minha doença, tudo acabará bem	1	2	3	4	5

Pontuação: _____

DATA: _____ D: 0

CÓDIGO

PHQ-9

Nas últimas 2 semanas, quantos dias você:	Nenhum dia	Menos de 7 dias	7 dias ou mais	Quase todos os dias
Teve pouco interesse ou pouco prazer em fazer as coisas?	0	1	2	3
Se sentiu para baixo, deprimido ou sem perspectiva?	0	1	2	3
Teve dificuldade para pegar no sono e permanecer dormindo, ou dormiu mais do que o de costume?	0	1	2	3
Se sentiu cansado ou com pouca energia?	0	1	2	3
Teve falta de apetite ou comeu demais?	0	1	2	3
Se sentiu mal consigo mesmo, ou achou que é um fracasso, ou achou que decepcionou sua família ou a você mesmo?	0	1	2	3
Teve dificuldade para se concentrar nas coisas (como ler jornal ou ver televisão)?	0	1	2	3
Teve lentidão para se movimentar ou falar (a ponto de outras pessoas perceberem) ou, ao contrário, esteve tão agitado que você ficava andando de um lado para o outro mais do que de costume?	0	1	2	3
Pensou em se ferir de alguma maneira ou que seria melhor estar morto?	0	1	2	3

Pontos de corte:

5-8: sintomas muito leves, subsindrômicos

≥9: rastreio positivo para episódio depressivo atual

9-14: episódio leve

15-19: episódio moderado

≥20: episódio grave

Fonte: Adaptado de Sensibilidade e especificidade do Patient Health Questionnaire-9 (PHQ-9) entre adultos da população geral, Rio de Janeiro: Cad Saude Publica, 2013; Screening and case finding for major depressive disorder using the Patient Health Questionnaire (PHQ-9): a meta-analysis. Gen Hosp Psychiatry, 2015.

Resultado: _____

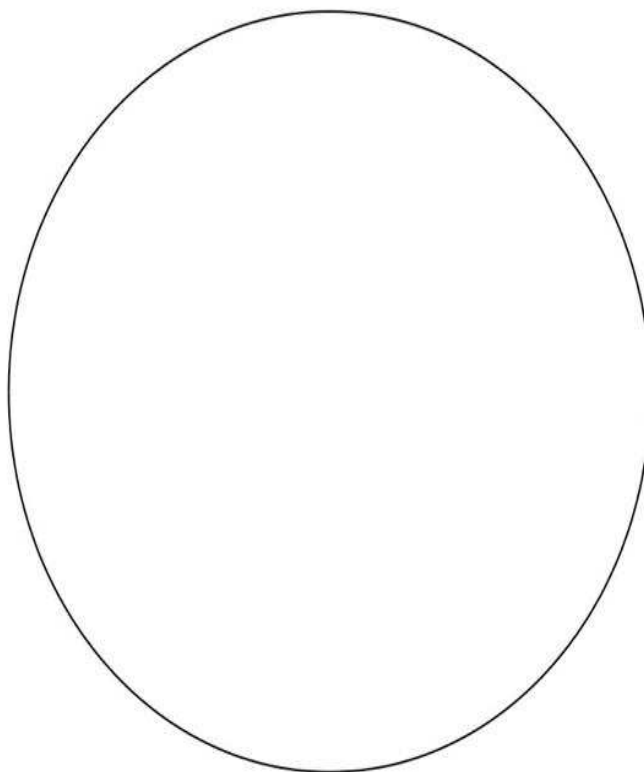
DATA: _____ D: 0

CÓDIGO

TESTE DO DESENHO DO RELÓGIO

INSTRUÇÕES: "Abaixo temos o mostrador de um relógio. Gostaria que o Sr. (a) colocasse os números dentro dele." Aguarde o sujeito terminar a tarefa e diga o seguinte: "Por favor, agora indique o horário 8h20m (oito horas e vinte minutos)." Certifique-se sempre que o paciente compreendeu as instruções antes de dar início à tarefa.

PONTUAÇÃO: Utilize a máscara. Posicione-a de modo que uma das linhas fique colocada a partir do centro do círculo até o número 12; caso o 12 tenha sido omitido, proceda da mesma maneira utilizando como base o 1. Desta forma as 8 fatias da máscara estarão posicionadas sobre o relógio, para que possa ser pontuado. Será dado um ponto para o posicionamento correto dos seguintes números: 1, 2, 4, 5, 7, 8, 10, 11 (será pontuado o número que estiver até sua metade incluída no oitavo correspondente). Um ponto será dado para o ponteiro pequeno indicando o 8 e um ponto será dado para o ponteiro grande indicando o 4. Total máximo de pontos = 10.



TOTAL = _____

DATA: _____ D: 0

CÓDIGO

ESCALA DE FRAGILIDADE DE EDMONTON

Domínio/Item	Respostas possíveis (pontuação)		
Cognição			
Teste do desenho do Relógio	Aprovado (0)	Reprovado – erros mínimos (1)	Reprovado – erros significativos (2)
Estado Geral de Saúde			
Nos últimos 12 meses, quantas vezes você foi internado?	Zero (0)	1-2 (1)	>2 (2)
De modo geral, como você descreveria a sua saúde?	Excelente, muito boa ou boa (0)	Razoável (1)	Ruim (2)
Independência funcional			
Em quantas das seguintes atividades você precisa de ajuda? Y Preparar refeição (cozinhar) Y transporte (locomoção de um lugar para outro) Y cuidar da casa (limpar/arrumar casa) Y fazer compras Y usar telefone Y levar roupa Y cuidar do dinheiro Y tomar remédios	0-1 (0)	2-4 (1)	5-8 (2)
Suporte Social			
Quando você precisa de ajuda, pode contar com a ajuda de alguém disposto e capaz de atender as suas necessidades?	Sempre (0)	Algumas vezes (1)	Nunca (2)
Uso de medicamentos			
Normalmente, você usa cinco ou mais remédios diferentes e receitados (pelo médico)?	Não (0)	Sim (1)	
Algumas vezes você esquece de tomar os seus remédios?	Não (0)	Sim (1)	
Nutrição			
Você tem perdido peso recentemente, de forma que suas roupas estão mais folgadas?	Não (0)	Sim (1)	

DATA: _____ D: 0

CÓDIGO

Humor			
Você se sente triste ou deprimido com frequência?	Não (0)	Sim (1)	
Continência			
Você tem problemas de perder o controle de urina sem querer?	Não (0)	Sim (1)	
Desempenho funcional			
Teste "levante e ande" cronometrado	0-10 segundos (0)	11-20 segundos (1)	>20 segundos (2)
Pontos de corte:			
0-4: não apresenta fragilidade			
5-6: aparentemente vulnerável			
7-8: fragilidade leve			
9-10: fragilidade moderada			
≥11: fragilidade grave			

Fonte: FABRÍCIO-WEHBE, Suzele Cristina Coelho et al. Reproducibilidad de la versión brasileña adaptada de la Edmonton Frail Scale para ancianos residentes en la comunidad. Revista Latino-Americana de Enfermagem, v. 21, p. 1330- 1336, 2013.

Resultado: _____

DATA: _____

D: 0 _____

CÓDIGO

CONTROLLED ORAL WORD ASSOCIATION TEST - Animais

Grupo Semântico

Instruções: pedir ao paciente para falar em voz alta o maior número de nomes de animais no intervalo de tempo de 1 minuto. A pontuação final corresponde ao número total de nomes corretos e não repetidos falados.

- | | | | |
|-----------|-----------|-----------|-----------|
| 1. _____ | 11. _____ | 21. _____ | 31. _____ |
| 2. _____ | 12. _____ | 22. _____ | 32. _____ |
| 3. _____ | 13. _____ | 23. _____ | 33. _____ |
| 4. _____ | 14. _____ | 24. _____ | 34. _____ |
| 5. _____ | 15. _____ | 25. _____ | 35. _____ |
| 6. _____ | 16. _____ | 26. _____ | 36. _____ |
| 7. _____ | 17. _____ | 27. _____ | 37. _____ |
| 8. _____ | 18. _____ | 28. _____ | 38. _____ |
| 9. _____ | 19. _____ | 29. _____ | 39. _____ |
| 10. _____ | 20. _____ | 30. _____ | 40. _____ |

Pontuação: _____

CONTROLLED ORAL WORD ASSOCIATION TEST - Frutas

Grupo Semântico

Instruções: pedir ao paciente para falar em voz alta o maior número de nomes de frutas no intervalo de tempo de 1 minuto. A pontuação final corresponde ao número total de nomes corretos e não repetidos.

- | | | | |
|-----------|-----------|-----------|-----------|
| 1. _____ | 11. _____ | 21. _____ | 31. _____ |
| 2. _____ | 12. _____ | 22. _____ | 32. _____ |
| 3. _____ | 13. _____ | 23. _____ | 33. _____ |
| 4. _____ | 14. _____ | 24. _____ | 34. _____ |
| 5. _____ | 15. _____ | 25. _____ | 35. _____ |
| 6. _____ | 16. _____ | 26. _____ | 36. _____ |
| 7. _____ | 17. _____ | 27. _____ | 37. _____ |
| 8. _____ | 18. _____ | 28. _____ | 38. _____ |
| 9. _____ | 19. _____ | 29. _____ | 39. _____ |
| 10. _____ | 20. _____ | 30. _____ | 40. _____ |

Pontuação: _____

EVA ANSIEDADE:

EVA DOR:

DATA: _____ D: 0

CÓDIGO

□	∩	∩	∩	∩	∩	∩	∩	∩
1	2	3	4	5	6	7	8	9

√2

□	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

∩	∩	∩	∩	∩	∩	∩	∩	∩

DATA: _____ D: 0

CÓDIGO

CONTROLLED ORAL WORD ASSOCIATION TEST - F**Grupo Fonético**

Instruções: pedir ao paciente para falar em voz alta o maior número de palavras que iniciem com a letra F, excluindo nomes próprios, no intervalo de tempo de 1 minuto. A pontuação final corresponde ao número total de palavras corretas e não repetidas faladas.

- | | | | |
|-----------|-----------|-----------|-----------|
| 1. _____ | 11. _____ | 21. _____ | 31. _____ |
| 2. _____ | 12. _____ | 22. _____ | 32. _____ |
| 3. _____ | 13. _____ | 23. _____ | 33. _____ |
| 4. _____ | 14. _____ | 24. _____ | 34. _____ |
| 5. _____ | 15. _____ | 25. _____ | 35. _____ |
| 6. _____ | 16. _____ | 26. _____ | 36. _____ |
| 7. _____ | 17. _____ | 27. _____ | 37. _____ |
| 8. _____ | 18. _____ | 28. _____ | 38. _____ |
| 9. _____ | 19. _____ | 29. _____ | 39. _____ |
| 10. _____ | 20. _____ | 30. _____ | 40. _____ |

Pontuação: _____

CONTROLLED ORAL WORD ASSOCIATION TEST - A**Grupo Fonético**

Instruções: pedir ao paciente para falar em voz alta o maior número de palavras que iniciem com a letra A, excluindo nomes próprios, no intervalo de tempo de 1 minuto. A pontuação final corresponde ao número total de palavras corretas e não repetidas faladas.

- | | | | |
|-----------|-----------|-----------|-----------|
| 1. _____ | 11. _____ | 21. _____ | 31. _____ |
| 2. _____ | 12. _____ | 22. _____ | 32. _____ |
| 3. _____ | 13. _____ | 23. _____ | 33. _____ |
| 4. _____ | 14. _____ | 24. _____ | 34. _____ |
| 5. _____ | 15. _____ | 25. _____ | 35. _____ |
| 6. _____ | 16. _____ | 26. _____ | 36. _____ |
| 7. _____ | 17. _____ | 27. _____ | 37. _____ |
| 8. _____ | 18. _____ | 28. _____ | 38. _____ |
| 9. _____ | 19. _____ | 29. _____ | 39. _____ |
| 10. _____ | 20. _____ | 30. _____ | 40. _____ |

Pontuação: _____

CONTROLLED ORAL WORD ASSOCIATION TEST - S**Grupo Fonético**

Instruções: pedir ao paciente para falar em voz alta o maior número de palavras que iniciem com a letra S, excluindo nomes próprios, no intervalo de tempo de 1 minuto. A pontuação final corresponde ao número total de palavras corretas e não repetidas faladas.

- | | | | |
|-----------|-----------|-----------|-----------|
| 1. _____ | 11. _____ | 21. _____ | 31. _____ |
| 2. _____ | 12. _____ | 22. _____ | 32. _____ |
| 3. _____ | 13. _____ | 23. _____ | 33. _____ |
| 4. _____ | 14. _____ | 24. _____ | 34. _____ |
| 5. _____ | 15. _____ | 25. _____ | 35. _____ |
| 6. _____ | 16. _____ | 26. _____ | 36. _____ |
| 7. _____ | 17. _____ | 27. _____ | 37. _____ |
| 8. _____ | 18. _____ | 28. _____ | 38. _____ |
| 9. _____ | 19. _____ | 29. _____ | 39. _____ |
| 10. _____ | 20. _____ | 30. _____ | 40. _____ |

Pontuação: _____

APÊNDICE F - Resultados D15 e D45

Variáveis delta dos testes neuropsicológicos e de atenção nos tempos D15 e D45, analisadas por análise de variância (ANOVA de uma via), com comparações múltiplas post hoc univariadas (valores de p).

Variável	Comparativo vs. Propofol	Propofol vs. Sevoflurano	Comparativo vs. Sevoflurano
δRT D15	0,094	0,232	0,272
δVRT D15	0,326	0,270	0,442
δCV D15	0,118	0,110	0,495
δOE D15	0,490	0,391	0,309
δCE D15	0,372	0,391	0,275
δCOWAT D15	0,307	0,416	0,241
δSDMT D15	0,181	0,500	0,060
δRT D45	0,067	0,283	0,185
δVRT D45	0,109	0,267	0,280
δCV D45	0,198	0,308	0,372
δOE D45	0,290	0,479	0,276
δCE D45	0,366	0,097	0,093
δCOWAT D45	0,333	0,466	0,306
δSDMT D45	0,473	0,272	0,290

Abreviações: δRT, delta do tempo de reação (*Reaction Time*); δVRT, delta da variabilidade do tempo de reação (*Variability of Reaction Time*); δCV, delta do coeficiente de variabilidade; δOE, delta dos erros por omissão (*Omission Errors*); δCE, delta dos erros por comissão (*Commission Errors*); δCOWAT, delta do **Controlled Oral Word Association Test**; δSDMT, delta do **Symbol Digit Modalities Test**; D15, avaliação realizada 15 dias após a cirurgia; D45, avaliação realizada 45 dias após a cirurgia.

Cálculo do delta: $\delta = (D0 - DX) / D0$, em que **D0** corresponde à avaliação basal (pré-operatória) e **DX** ao momento de seguimento avaliado (D15 ou D45).

ANOVA: análise de variância de uma via. Valores de p inferiores a 0,05 foram considerados estatisticamente significativos.

ANEXO A - Parecer Consubstanciado do CEP-HUGG

UNIRIO - HOSPITAL
UNIVERSITÁRIO GAFFREE E
GUINLE / HUGG- UNIRIO



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ALTERAÇÕES COGNITIVAS RELACIONADAS À TÉCNICA ANESTÉSICA

Pesquisador: CAROLINA RIBEIRO MELLO

Área Temática:

Versão: 1

CAAE: 54581221.0.0000.5258

Instituição Proponente: Hospital Universitário Gaffree e Guinle/HUGG/UNIRIO

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.187.287

Apresentação do Projeto:

Trata-se do projeto de pesquisa "ALTERAÇÕES COGNITIVAS RELACIONADAS À TÉCNICA ANESTÉSICA", ensaio clínico randomizado, unicêntrico, cego visando a comparação de entre duas técnicas anestésicas diferentes para anestesia geral e um grupo controle de pacientes que não foram submetidos a cirurgia que compara incidência de disfunção cognitiva pós operatória (DCPO).

Objetivo da Pesquisa:

Objetivo Primário: Avaliar a disfunção cognitiva pós-operatória (DCPO) em relação à escolha da técnica anestésica, em cirurgias de médio porte.

Objetivo Secundário: Avaliar a DCPO em função da técnica anestésica, de acordo com os seguintes parâmetros:

Alerta intrínseco-Capacidade de focar e sustentar a atenção,

Inibição de respostas inadequadas no pós-operatório.

Avaliação dos Riscos e Benefícios:

Riscos:

O riscos são os mesmos já existentes no procedimento proposto. Se trata de um estudo observacional, com técnicas anestésicas e cirúrgicas usuais na literatura. Riscos relacionados à quebra de confidencialidade foram considerados e esforços serão feitos para minimizá-los.

Benefícios:

Balisar escolha de futura técnicas anestésicas, considerando risco de DCPO.

Endereço: Rua Mariz e Barros nº 775

Bairro: Tijuca

CEP: 22.270-004

UF: RJ

Município: RIO DE JANEIRO

Telefone: (21)2264-5317

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E-mail: cephugg@gmail.com

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UNIVERSITÁRIO GAFFRÉE E
GUINLE / HUGG- UNIRIO**



Continuação do Parecer: 5.187.287

Comentários e Considerações sobre a Pesquisa:

Alterações de cognição relacionadas a anestesia estão sendo alvo de estudos recentes, a começar pela sua definição, onde a DCPO tem sido investigada, como uma desordem sutil dos processos do pensamento que pode influenciar domínios isolados da cognição, tais como atenção, memória verbal, memória visual, compreensão da linguagem, e função executiva que ocorrem em 30 dias a 12 meses de pós-operatório que não se justifica por outra condição clínica. A sua incidência pode variar entre 10-40%. Por se apresentar como uma manifestação clínica muito sutil, só pode ser diagnosticada por testes neuropsicológicos, que são realizados antes e após a exposição à anestesia. Alterações cognitivas inferiores a 30 dias são classificadas como atraso de recuperação cognitiva. A disfunção pode permanecer como uma desordem definitiva. Diferentemente do quadro agudo de delirium, a DCPO não afeta o nível de consciência e este diagnóstico ainda não consta nas listas de doenças CID-10. É possível considerar a DCPO como um distúrbio neurocognitivo de etiologia não especificada dentro dos limites do Diagnostic and Statistical Manual of Mental Disorders (DSM V), pouco difundido entre psiquiatras, neurologistas e neuropsicólogos. Seu diagnóstico baseia-se na queda de um desvio padrão em pelo menos dois testes neuropsicológicos avaliando diferentes domínios da cognição em até 90 dias de pós-operatório associado a alteração de biomarcadores de lesão neuronal. O presente estudo busca avaliar a influência da escolha técnica anestésica na

incidência de alterações atencionais pós-operatórias imediatas e em até 30 dias de pós-operatório.

Considerações sobre os Termos de apresentação obrigatória:

Termos obrigatórios apresentados conforme normas.

Recomendações:

Sem recomendações.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_P ROJETO_1878729.pdf	23/12/2021 11:47:29		Aceito

Endereço: Rua Mariz e Barros nº 775

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Continuação do Parecer: 5.187.287

TCLE / Termos de Assentimento / Justificativa de Ausência	modelotcledcpo.pdf	23/12/2021 11:47:01	CAROLINA RIBEIRO MELLO	Aceito
Projeto Detalhado / Brochura Investigador	Brochura.pdf	23/12/2021 11:46:52	CAROLINA RIBEIRO MELLO	Aceito
Outros	Termodeanuencialapia.pdf	23/12/2021 11:46:36	CAROLINA RIBEIRO MELLO	Aceito
Orçamento	orcamentodcpo.pdf	23/12/2021 11:46:12	CAROLINA RIBEIRO MELLO	Aceito
Declaração de concordância	Termodeanuenciacentrocirurgico.pdf	23/12/2021 11:45:57	CAROLINA RIBEIRO MELLO	Aceito
Declaração de Pesquisadores	Termopesquisadora.pdf	23/12/2021 11:45:43	CAROLINA RIBEIRO MELLO	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Termodecompromissolapia.pdf	23/12/2021 11:45:28	CAROLINA RIBEIRO MELLO	Aceito
Declaração de Instituição e Infraestrutura	Termodeanuenciadirecao.pdf	23/12/2021 11:45:16	CAROLINA RIBEIRO MELLO	Aceito
Cronograma	cronogramacep.pdf	23/12/2021 11:45:00	CAROLINA RIBEIRO MELLO	Aceito
Folha de Rosto	Folhaderostrocep.pdf	23/12/2021 11:44:47	CAROLINA RIBEIRO MELLO	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

RIO DE JANEIRO, 27 de Dezembro de 2021

Assinado por:
Jorge Francisco da Cunha Pinto
(Coordenador(a))

Endereço: Rua Mariz e Barros nº 775

Bairro: Tijuca

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