Dinámicas autonómicas, neurofisiológicas y experienciales en el delirium asociado a sepsis: una aproximación desde la cognición corporeizada

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“The body is our general medium for having a world.”

Merleau Ponty

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RESUMEN

El delirium es un síndrome neuropsiquiátrico agudo caracterizado por alteraciones fluctuantes de la atención, la conciencia y la cognición, altamente prevalente en pacientes hospitalizados y particularmente frecuente en el contexto de la sepsis, donde se manifiesta como delirium asociado a sepsis (SAD). Este cuadro constituye la expresión clínica más frecuente de la disfunción cerebral aguda en la sepsis y se asocia con una mayor mortalidad, estancias hospitalarias prolongadas y un deterioro cognitivo y funcional posterior. Dentro de este continuo clínico se incluye el delirium subsindromal (SSD), una forma incompleta del cuadro que comparte mecanismos fisiopatológicos y relevancia clínica, y se asocia con mayor vulnerabilidad cognitiva y funcional. En conjunto, el SAD y el SSD configuran un espectro de alteraciones cerebrales agudas en pacientes con sepsis.

Desde una perspectiva neurobiológica, el SAD y el SSD se asocian con alteraciones de la función cerebral, incluyendo cambios en la neurotransmisión, la conectividad funcional y la organización de las redes cerebrales, así como en el enlentecimiento oscilatorio. Sin embargo, los enfoques centrados exclusivamente en el sistema nervioso central no explican por completo la variabilidad clínica ni la fluctuación sintomática observadas a lo largo del continuo SAD–SSD, lo que sugiere la necesidad de marcos integradores.

Esta tesis doctoral se inscribe en el marco de la cognición corporeizada y de la distinción entre cuerpo vivo y cuerpo vivido propuesta por Thomas Fuchs, con el propósito de comprender el SAD y el SSD como fenómenos que comprometen la

integración cerebro–cuerpo durante la enfermedad crítica. Desde este enfoque, el delirium se concibe como un proceso que involucra alteraciones del cuerpo vivo, expresadas en la regulación autonómica y la dinámica neurofisiológica, junto con transformaciones del cuerpo vivido, manifestadas en la experiencia corporal y cognitiva. En coherencia con este marco, la tesis analiza cómo estas dimensiones fisiológicas y experienciales se articulan en el SAD y el SSD durante el delirium.

La tesis se desarrolló en formato de compendio de tres artículos. El primero correspondió a una revisión de alcance orientada a caracterizar las alteraciones del sistema nervioso autónomo reportadas en pacientes hospitalizados con delirium. Los estudios incluidos describieron alteraciones cardiovasculares, como cambios en la variabilidad de la frecuencia cardíaca, aumento de la variabilidad de la presión arterial y disminución de la presión arterial media, junto con reducción de la velocidad de dilatación pupilar, alteraciones gastrointestinales asociadas a desequilibrios de la microbiota intestinal y modificaciones en neurotransmisores periféricos.

El segundo artículo es un estudio observacional que examinó la integración corazón–cerebro mediante potenciales evocados por latidos cardíacos (HEP) en pacientes hospitalizados con SAD, SSD y sin delirium, en reposo. Los resultados demostraron la factibilidad de obtener la señal HEP en contexto clìnico y mostraron diferencias en la modulación dependiente del estado (ojos abiertos–ojos cerrados) en pacientes con SAD y SSD, sugiriendo que los HEP son sensibles para explorar variaciones en la integración viscero–cerebral. Estos hallazgos se describieron junto

con un menor desempeño en pruebas cognitivas al alta en pacientes con SAD y SSD.

El tercer artículo correspondió a un estudio cualitativo basado en teoría fundamentada, que exploró la experiencia corporal y cognitiva de pacientes con sepsis, SAD y SSD mediante entrevistas semiestructuradas. Los relatos describieron alteraciones del cuerpo vivido, incluyendo despersonalización somática, pérdida de control corporal, dolor y malestar, así como alucinaciones visuales, distorsión de la realidad, desorientación y dificultades de comunicación.

En conjunto, los resultados sugieren que el SAD y el SSD pueden comprenderse como expresiones de un mismo continuo de alteración de la integración cerebro–cuerpo en la sepsis. Este enfoque permite integrar dimensiones neurofisiológicas, autonómicas y experienciales, y aporta un marco para el desarrollo de estrategias de monitoreo y cuidado en contextos críticos.

ABSTRACT

Delirium is an acute neuropsychiatric syndrome characterized by fluctuating disturbances of attention, consciousness, and cognition. It is highly prevalent among hospitalized patients and particularly frequent in the context of sepsis, where it manifests as sepsis-associated delirium (SAD). SAD represents the most common clinical expression of acute brain dysfunction in sepsis and is associated with increased mortality, prolonged hospital stays, and subsequent cognitive and functional decline. Within this clinical continuum, subsyndromal delirium (SSD) is recognized as an incomplete form of the syndrome that shares pathophysiological mechanisms and clinical relevance and is associated with increased cognitive and functional vulnerability. Together, SAD and SSD constitute a spectrum of acute cerebral alterations in patients with sepsis.

From a neurobiological perspective, SAD and SSD are associated with alterations in brain function, including changes in neurotransmission, functional connectivity, and the organization of brain networks, as well as oscillatory slowing. However, approaches focused exclusively on the central nervous system do not fully account for the clinical variability or symptom fluctuation observed across the SAD–SSD continuum, highlighting the need for more integrative conceptual frameworks.

This doctoral thesis is grounded in the framework of embodied cognition and in the distinction between the living body and the lived body proposed by Thomas Fuchs, with the aim of understanding SAD and SSD as conditions that compromise brain–body integration during critical illness. From this perspective, delirium is

conceptualized as a process involving alterations of the living body—expressed through autonomic regulation and neurophysiological dynamics—together with transformations of the lived body, manifested in bodily and cognitive experience. In line with this framework, the thesis examines how these physiological and experiential dimensions are articulated in SAD and SSD during delirium.

The thesis was conducted as a compendium of three complementary articles. The first article consisted of a scoping review aimed at characterizing autonomic nervous system alterations reported in hospitalized patients with delirium. The included studies described cardiovascular alterations such as changes in heart rate variability, increased blood pressure variability, and reduced mean arterial pressure, along with reduced pupillary dilation velocity, gastrointestinal alterations associated with imbalances in the intestinal microbiota, and changes in peripheral neurotransmitter levels.

The second article was an observational study that examined heart–brain integration through the analysis of heart-evoked potentials (HEP) in hospitalized patients with SAD, SSD, and without delirium, under resting-state conditions. The results demonstrated the feasibility of acquiring the HEP signal in this clinical setting and showed differences in state-dependent modulation (eyes open–eyes closed) in patients with SAD and SSD, indicating that HEPs can be used to explore variations in viscerocortical integration. These findings were accompanied by lower cognitive performance at hospital discharge in patients with SAD and SSD.

The third article corresponded to a qualitative study based on grounded theory, which explored the bodily and cognitive experiences of patients with sepsis, SAD, and SSD through semi-structured interviews. Participants described alterations of the lived body, including somatic depersonalization, loss of bodily control, pain and discomfort, as well as cognitive experiences such as visual hallucinations, distorted reality, disorientation, and communication difficulties.

Overall, the results suggest that SAD and SSD can be understood as expressions of a single continuum of altered brain–body integration in sepsis. This embodied cognition approach enables the integration of neurophysiological, autonomic, and experiential dimensions and provides a framework for the development of monitoring and care strategies in critical care settings.

I. INTRODUCCION

Delirium en pacientes sépticos

La sepsis se define como una disfunción orgánica potencialmente mortal causada por una respuesta desregulada del huésped ante una infección (Singer et al., 2016). Esta disfunción orgánica se identifica por un aumento agudo de ≥2 puntos en el puntaje Sepsis-Related Organ Failure Assessment (SOFA), lo que refleja un riesgo de mortalidad hospitalaria aproximado al 10% (Singer et al., 2016). A nivel mundial, la sepsis constituye un grave problema de salud pública, con una incidencia estimada de 48,9 millones de casos y 11 millones de muertes anuales (Fleischmann et al., 2016; Rudd et al., 2020). Entre un 25% y un 50% de los pacientes con sepsis desarrollan alteraciones neurocognitivas agudas, siendo el delirium asociado a sepsis (SAD, por sus siglas en inglés, *Sepsis-Associated Delirium*) su manifestación más frecuente y clínicamente relevante (Atterton et al., 2020; Chung et al., 2020; Tokuda et al., 2023). El SAD se caracteriza por un inicio agudo y curso fluctuante, con déficits de atención y cognición, alteraciones del ritmo circadiano, disregulación emocional y cambios psicomotores, que reflejan una disfunción cerebral difusa (Tokuda et al., 2023). Este cuadro se asocia con una mayor mortalidad, una estancia hospitalaria prolongada y un deterioro funcional persistente (Girard et al., 2010; Pandharipande et al., 2013; Salluh et al., 2015; Tokuda et al., 2023). En este continuo clínico también se incluye el delirium subsindromal (SSD), una forma atenuada que comparte características cognitivas con el delirium y se relaciona con peores desenlaces y con deterioro cognitivo transitorio tras el alta hospitalaria (Paulino et al., 2023; Serafim et al., 2017).

La fisiopatología del SAD es multifactorial. Involucra procesos de neuroinflamación, disfunción endotelial, alteraciones microcirculatorias y desequilibrio de la neurotransmisión (Hughes et al., 2013; Semmler et al., 2007; Sharshar et al., 2004) . Las citocinas proinflamatorias activan el endotelio cerebral y las células microgliales, incrementando la permeabilidad de la barrera hematoencefálica y generando estrés oxidativo (Chung et al., 2020). Paralelamente, se plantea la posible disfunción de la neurotransmisión, con hipofunción colinérgica y desregulación dopaminérgica y noradrenérgica, que favorece las alteraciones de atención, cognición y regulación afectiva propias del delirium (Pandharipande et al., 2009; Pinheiro da Silva et al., 2013). En la dinámica electrofisiología, el SAD se caracteriza por alteraciones agudas en la conectividad funcional y en la actividad eléctrica cortical, con enlentecimiento de los patrones de actividad eléctrica cerebral medidos mediante electroencefalografía (EEG), reducción de las oscilaciones alfa–beta (12–30 Hz) y aumento de la conectividad en bandas theta (3.5–7.5 Hz) y delta (0.1–4 Hz) (Fleischmann et al., 2016; Jacobson et al., 1993; Numan et al., 2019; van Dellen et al., 2014). Estos patrones reflejan una disminución de la sincronía neuronal y de la eficiencia funcional de las redes corticales (Morandi et al., 2012; Numan et al., 2019).

La sepsis es una disfunción orgánica grave causada por una respuesta inflamatoria desregulada, con alta incidencia y mortalidad mundial. Entre un 25% y 50% de los pacientes desarrollan SAD y SSD, caracterizado por fluctuaciones cognitivas y atencionales, mayor mortalidad y secuelas persistentes. Este cuadro refleja una alteración neuroinflamatoria y de la conectividad cortical, que evidencia una disrupción global en la integración cuerpo–cerebro.

Cognición corporeizada

El marco de la cognición corporeizada (embodied cognition) y la enacción (Gallagher & Payne, 2015; Varela et al., 2016) ofrece una perspectiva para comprender la relación entre cuerpo y cognición en el delirium. Desde esta visión, los procesos cognitivos no constituyen una instancia separada, sino un proceso dinámico que emerge de la interacción continua entre el cerebro, el cuerpo y el entorno. La cognición se entiende como una acción situada, distribuida entre múltiples niveles biológicos y contextuales (A. D. Wilson & Golonka, 2013). Diversos autores han sistematizado sus principios fundamentales: i) carácter anti-internalista de la cognición, ii) dependencia constitutiva del cuerpo, iii) anclaje corporal del significado y iv) extensión activa de la cognición al entorno (Farina, 2021; Fuchs, 2020; Shapiro, 2007).

La Enacción concibe a los organismos como sistemas autónomos y estructuralmente determinados, cuya continuidad depende de procesos de acoplamiento con el entorno para la construcción de sentido. La cognición surge, así, de estas interacciones recursivas que vinculan dimensiones fisiológicas, neurales, afectivas y sociales, dando forma a la experiencia (Lux et al., 2021). En esta línea, Thomas Fuchs (2020) profundiza en la dimensión encarnada de la cognición distinguiendo entre el cuerpo vivo (i.e., *living body*), correspondiente al organismo fisiológico y neurovisceral que sostiene la vida, y el cuerpo vivido (i.e., *lived body*), que constituye la dimensión fenomenológica desde la cual se percibe y se actúa.

El cuerpo vivo constituye el soporte biológico que posibilita la experiencia mediante la integración dinámica entre cerebro y cuerpo, mientras que el cuerpo vivido representa el trasfondo desde el cual se interpreta, se siente y se orienta la acción en el mundo. Ambos aspectos conforman una unidad circular, en la que los procesos

biológicos y experienciales se co-determinan mutuamente, redefiniendo el llamado "problema cuerpo–cuerpo" al mostrar que la experiencia subjetiva emerge de la interacción recíproca entre lo fisiológico y lo experiencial.

Dentro de este marco, Fuchs describe que esta unidad cuerpo vivo–cuerpo vivido se articula mediante dos formas complementarias de circularidad. La circularidad estructural se refiere a que la organización fisiológica del cuerpo vivo, sus ritmos autonómicos, su regulación *hemodinámica* y su integración viscero-cerebral constituyen la base que posibilita toda experiencia. La circularidad causal, en cambio, describe cómo la experiencia emergente del cuerpo vivido influye de manera recursiva sobre la regulación corporal, modulando la postura, la respiración, el tono autonómico, el nivel de alerta y los modos de interacción con el entorno. Desde este enfoque, la conciencia no es un contenido interno representado en el cerebro, sino una resonancia dinámica entre cuerpo, cerebro y mundo, sostenida por estas circularidades que integran y reconfiguran de manera continua la relación entre fisiología y experiencia (Fuchs, 2020).

Durante el SAD y el SSD, estas circularidades pueden volverse frágiles: alteraciones en la regulación autonómica, la neuroinflamación y los cambios en la integración viscero-cerebral pueden modificar las condiciones que sostienen la experiencia, mientras que las transformaciones en la vivencia perceptual y corporal repercuten sobre la dinámica fisiológica. Esta desorganización puede entenderse como una pérdida transitoria de la coherencia cuerpo vivo–cuerpo vivido que sostiene la conciencia situada.

Esta tesis se inscribe en este marco y busca explorar los aspectos del cuerpo vivo, examinando cómo se integran los cambios neurofisiológicos observables (particularmente las dinámicas cuerpo-cerebro) en pacientes con SAD y SSD, y

cómo estos se relacionan con las manifestaciones del cuerpo vivido, es decir, con su experiencia subjetiva.

Cuerpo vivo: Integración viscero-cerebral en el delirium

Desde la perspectiva de la cognición corporeizada, el cuerpo vivo constituye la base fisiológica y autorreguladora que sostiene los procesos vitales y la actividad cerebral (Fuchs, 2020). Esta dimensión corresponde a la circularidad estructural, dado que la organización autonómica, visceral y cortical configura las condiciones que posibilitan la experiencia y orientan la percepción y la acción en el mundo. Su funcionamiento depende de redes dinámicas que mantienen la homeostasis y permiten la adaptación al entorno.

Entre estas redes, la integración entre las vísceras y el cerebro ocupa un lugar central: órganos como el corazón y el intestino envían información continua hacia estructuras subcorticales y corticales, formando un eje viscero–cerebral esencial para la estabilidad fisiológica (Azzalini et al., 2019; Craig, 2002; Critchley & Harrison, 2013; Engelen et al., 2023). El sistema nervioso autónomo (SNA) participa en esta integración. Coordinando funciones vitales como la frecuencia cardíaca, la respiración, la presión arterial, la digestión y la actividad glandular (Debnath et al., 2021; Zygmunt & Stanczyk, 2010), el SNA opera mediante vías ascendentes que que se integran en el sistema nerviosos central (SNC) los estados corporales (Quigley et al., 2021) y vías descendentes, que ajustan su funcionamiento (Candia-Rivera, 2022). Sus ramas simpática y parasimpática actúan de manera complementaria, y su organización funcional se articula con la red autonómica central (central autonomic network), que incluye el tronco encefálico, el hipotálamo, la ínsula y la corteza cingulada anterior (Critchley & Harrison, 2013; Ferraro et al.,

2022). Este circuito viscero-cerebral integra las señales interoceptivas con la actividad cortical, posibilitando el monitoreo de los estados corporales(Azzalini et al., 2019; Craig, 2002; Critchley & Harrison, 2013; Engelen et al., 2023).

En el SAD y SSD, algunos estudios han mostrado alteraciones del SNA, reflejadas en la variabilidad de la frecuencia cardíaca (HRV), la presión arterial y la reactividad pupilar (Maldonado, 2018; Watne et al., 2016). Estos cambios podrían asociarse a cambios entre la actividad simpática y parasimpática. Aunque estos hallazgos sugieren una desregulación del cuerpo vivo, la literatura carece de una organización clara sobre qué componentes específicos del SNA se alteran durante el delirium y cómo estos cambios se relacionan con los mecanismos cerebrales.

La integración viscero–cerebral también se puede estudiar a través de la actividad cortical modulada por señales cardíacas. Una forma de evaluar esta integración —núcleo de la circularidad estructural del cuerpo vivo— es analizar la modulación que el latido cardíaco ejerce sobre la señal EEG. En este contexto, los potenciales relacionados al corazón (*Heart-Evoked Potentials*, HEP) se interpretan como un índice neurofisiológico de la comunicación viscero–cerebral, ya que se obtienen alineando la señal EEG con el complejo R del electrocardiograma (ECG) y reflejan la sensibilidad cortical a los impulsos cardíacos (Coll et al., 2020; Montoya et al., 1993)). Estudios recientes han mostrado que los HEP se relacionan con ajustes en la regulación autonómica, con la conciencia interoceptiva (Coll et al., 2020; Park et al., 2018; Park & Blanke, 2019), y cambios en estados cerebrales inducidos por anestesia, daño neurológico o fluctuaciones de conciencia (Candia-Rivera et al., 2021; Candia-Rivera & Machado, 2023; Virjee et al., 2024).

A pesar de su potencial, no existen estudios que examinen los HEP en pacientes con SAD o SSD ni investigaciones que integren simultáneamente el EEG y el ECG

en este contexto. Esta ausencia limita la comprensión de cómo las alteraciones del cuerpo vivo, en particular las disrupciones autonómicas y viscero-corticales, se expresan en la actividad cerebral durante la enfermedad crítica. Dado que los HEP reflejan la sensibilidad cortical a señales cardíacas y se han asociado a la regulación autonómica y a estados de conciencia alterados, su estudio podría aportar un marcador neurofisiológico de la integración viscero–cerebral, complementario a la evaluación clínica del delirium.

Cuerpo vivido en el delirium: evidencia cualitativa

La comprensión de cómo se vive el delirium desde la perspectiva del paciente sigue siendo limitada. Los estudios cualitativos disponibles describen experiencias relacionadas con la interacción con el equipo de enfermería (Granberg et al., 1998; Harding, 2005), desorientación temporal (Granberg et al., 1999; Whitehorne et al., 2015), recuerdos fragmentados y preocupaciones respecto de la seguridad personal (Whitehorne et al., 2015). Sin embargo, gran parte de esta evidencia proviene de pacientes postquirúrgicos o sometidos a ventilación mecánica, lo que dificulta extrapolar estos hallazgos a personas con sepsis, cuya fisiopatología, caracterizada por neuroinflamación, disfunción autonómica y alteraciones en redes cerebrales, podría generar formas particulares de perturbación corporal y cognitiva. Además, la mayoría de estos estudios se ha centrado en la experiencia global del delirium, sin indagar cómo los pacientes vivieron los cambios corporales y cognitivos durante el episodio ni cómo esos cambios fisiológicos fueron experimentados.

Desde el marco de la cognición corporeizada y la distinción entre cuerpo vivo y cuerpo vivido propuesta por Fuchs (2020), esta brecha adquiere mayor relevancia. La experiencia consciente emerge de una circularidad estructural en la que los

procesos del cuerpo vivo (ritmos autonómicos, dinámica visceral e integración viscero-cerebral) constituyen la base que posibilita la experiencia. A la vez, mediante circularidad causal, la vivencia subjetiva influye recursivamente sobre la regulación corporal, modulando patrones de respiración, tono autonómico y modos de estar en el entorno (Fuchs, 2020). Desde esta perspectiva, comprender el delirium exige atender tanto a los cambios fisiológicos que posibilitan la experiencia como a las transformaciones del cuerpo vivido que pueden reorganizar dicha dinámica.

Aplicado al SAD, este marco permite comprender que la desorganización autonómica y los cambios en la dinámica cerebro–cuerpo no solo acompañan el trastorno, sino que también pueden participar en la alteración del cuerpo vivido durante el episodio. Mientras se han descrito cambios electroencefalográficos y ciertas alteraciones autonómicas en sepsis, persisten varias brechas en el conocimiento actual:

i) no existe una síntesis organizada de los cambios del sistema nervioso autónomo (SNA) en delirium;

ii) no se han realizado estudios que examinen los Heart-Evoked Potentials (HEP) en delirium, a pesar de que permiten evaluar cómo la actividad cardíaca modula la actividad cortical y, potencialmente, la coherencia del cuerpo vivido en condiciones de inestabilidad fisiológica;

iii) tampoco existen estudios que analicen cómo la desregulación fisiológica se relaciona con las modificaciones en la experiencia corporal reportada por los pacientes.

En conjunto, la evidencia disponible es insuficiente para comprender cómo se articulan los cambios del cuerpo vivo con la vivencia del cuerpo vivido en el delirium asociado a sepsis. Esta falta de integración teórica y empírica constituye una brecha

que requiere investigación orientada a comprender cómo los pacientes experimentan los cambios corporales y cognitivos durante el delirium y cómo estos se relacionan con la dinámica viscero–cerebral.

Limitaciones y brechas

La evidencia existente presenta varias limitaciones que justifican estudiar el delirium desde una perspectiva de cognición corporeizada. Primero, los enfoques autonómico, cortical y experienciales se han desarrollado por separado, lo que impide comprender cómo cada dimensión contribuye al fenómeno. La investigación fisiológica se ha centrado en indicadores aislados y los estudios cualitativos en la experiencia subjetiva, sin integrar información del cuerpo vivo, en los mismos participantes. Segundo, no existen estudios multimodales en pacientes críticos que registren de manera simultánea señales viscerales (como actividad cardíaca) y actividad cortical, lo que limita la descripción de la dinámica viscero–cerebral durante la enfermedad aguda. Tercero, persiste una brecha entre la medición fisiológica y la comprensión experiencial, dificultando analizar cómo los cambios del cuerpo vivo (incluidas las alteraciones autonómicas o cardio–corticales) se relacionan con transformaciones del cuerpo vivido durante el delirium. Este vacío no apunta a la necesidad de un modelo integrador, sino de investigaciones que permitan articular estas capas del fenómeno desde un enfoque corporeizado.

En el SAD y SSD, se observan alteraciones autonómicas y cardio–corticales junto a experiencias de desconexión y desorientación; sin embargo, estas dimensiones han sido estudiadas por separado. Esta separación evidencia una brecha conceptual y metodológica que requiere estudios que integren ambas capas del fenómeno desde la cognición corporeizada. La presente tesis aborda este vacío mediante el análisis

complementario de cambios fisiológicos y experiencias del delirium, con el fin de avanzar hacia una comprensión más integrada del trastorno.

II. PREGUNTA DE INVESTIGACIÓN

¿Cómo es el proceso de cognición corporeizada en personas con delirium asociado a sepsis, considerando las manifestaciones del cuerpo vivo (alteraciones autonómicas y neurofisiológicas) y las manifestaciones del cuerpo vivido (experiencia corporal y cognitiva)?

III. OBJETIVOS

OBJETIVO GENERAL

Analizar los componentes de la cognición corporeizada del delirium en personas con sepsis, considerando las alteraciones autonómicas y neurofisiológicas del cuerpo vivo y las experiencias corporales y cognitivas del cuerpo vivido.

OBJETIVOS ESPECÍFICOS

1. Describir y organizar la evidencia existente sobre los cambios del sistema nervioso autónomo en el delirium. (Cuerpo vivo – regulaciones autonómicas)
2. Examinar la dinámica corazón–cerebro mediante HEP en pacientes sépticos con y sin delirium. (Cuerpo vivo – modulación neurofisiológica)
3. Explorar las experiencias corporales y cognitivas de personas que han vivido delirium, identificando los significados atribuidos a esos cambios. (Cuerpo vivido – experiencia subjetiva)

IV. PRESENTACION DE ARTICULOS DESARROLLADOS DURANTE EL PROCESO DOCTORAL

ARTÍCULO 1. *Characterizing autonomic nervous system alterations in hospitalized patients with delirium: A scoping review.*

(En proceso de corrección en la revista Autonomic Neuroscience: Basic and Clinical, Q1)

1) Pregunta, objetivo y relación con la tesis

El primer artículo se desarrolla a partir de la pregunta: ¿Qué cambios específicos en la actividad del SNA se han identificado en estos pacientes con delirio? Una pregunta secundaria explora: ¿Qué métodos se han utilizado para estudiar las alteraciones del SNA? El objetivo que guía este trabajo es sintetizar y organizar la evidencia disponible sobre cambios autonómicos en el delirium, abarcando la variabilidad cardíaca, la presión arterial, la respiración, el reflejo pupilar y las funciones exocrinas, con el fin de identificar vacíos conceptuales y metodológicos.

Este artículo responde al objetivo global de la tesis al abordar el nivel más basal del cuerpo vivo. Proporciona el mapa fisiológico inicial de la corporización del delirium y establece brechas en el conocimiento sobre los cambios en el SNA en pacientes con delirium. Así, constituye el punto de partida para comprender cómo la regulación visceral puede alterarse en pacientes con delirium y contribuir a la ruptura de la relación cuerpo–cerebro–conciencia.

2) Diseño y metodología, con justificación teórica y técnica

Este estudio adopta un diseño de scoping review siguiendo las directrices metodológicas del Joanna Briggs Institute (JBI) y apoyándose en el marco

conceptual de Arksey y O'Malley, posteriormente ampliado por Levac y colaboradores (Peters et al., 2020; Tricco et al., 2018).

La elección técnica de esta metodología se fundamenta en la marcada heterogeneidad del campo: existen estudios de naturaleza fisiológica, clínica, neuropsicológica y electrofisiológica, con indicadores autonómicos muy diversos y poco comparables entre sí. Una revisión sistemática tradicional no sería adecuada, dado que no existe homogeneidad en las medidas ni un marco robusto que permita una síntesis cuantitativa. En cambio, una scoping review permite mapear, agrupar, describir y clarificar ámbitos conceptuales dispersos.

Desde la perspectiva teórica de la cognición corporeizada, esta metodología permite analizar el cuerpo vivo como base fisiológica del delirium, ya que las variaciones en el SNA representan el nivel elemental de la relación víscero–cerebral.

3) Sinopsis del artículo y lugar en la secuencia de la tesis

Este artículo ofrece una revisión organizada del conocimiento existente sobre las alteraciones del sistema nervioso autónomo (SNA) en el delirium. Identifica áreas del SNA evaluadas, las formas de registro y los hallazgos encontrados, buscando evidenciar las formas de organizar estas alteraciones en pacientes con delirium.

En la secuencia de la tesis, este artículo desempeña un papel introductorio. Delimita el nivel autonómico como la primera capa del cuerpo vivo y establece la base fisiológica a partir de la cual se desarrollan los análisis posteriores. Esto prepara el terreno para el Artículo 2, centrado en la integración neurofisiológica entre corazón y cerebro.

ARTÍCULO 2 — *Heartbeat-evoked potentials in sepsis - associated delirium: exploring heart–brain integration*

(Borrador formato Revista)

1) Pregunta, objetivo y relación con la tesis

El segundo artículo responde a la pregunta: ¿Cómo se integra la señal cardíaca en la actividad cortical de pacientes sépticos con y sin delirium?

Su objetivo es analizar los HEP y la actividad EEG para describir la modulación cardiocortical en sepsis, comparando la dinámica viscero–cerebral según presencia o ausencia de delirium. Este artículo se alinea con el objetivo general de la tesis al abordar otro nivel del cuerpo vivo: el acoplamiento corazón–cerebro. Además, proporciona evidencia fisiológica explícita de que el delirium puede entenderse como una alteración en la integración viscero–cerebral.

2) Diseño y metodología, con justificación teórica y técnica

El estudio emplea un diseño observacional con registro simultáneo de EEG y ECG en condiciones de ojos abiertos (EO) y ojos cerrados (EC), aplicado a pacientes hospitalizados por sepsis con focos abdominales, respiratorios o renales. Esta elección metodológica permite obtener HEP, un marcador que permite estudiar la integración viscero–cerebral. Este diseño permite evaluar las diferencias entre grupos clínicos. Teóricamente, los HEP representan un índice para estudiar el cuerpo vivo desde la cognición corporeizada, en este caso durante el periodo clínico en el cual es más probable observar delirium, es decir, entre el primer y el tercer día,

ya que capturan la integración viscero–cerebral. La inexistencia previa de estudios HEP sobre el delirium asociado a la sepsis refuerza la justificación del trabajo.

3) Sinopsis del artículo y lugar en la secuencia de la tesis

Este artículo profundiza en un mecanismo específico del cuerpo vivo: la integración corazón–cerebro, evaluada mediante HEP en pacientes con sepsis en etapa aguda. A partir de un registro simultáneo EEG–ECG realizado dentro de las primeras 72 horas de hospitalización, se examina cómo la modulación cortical de las señales cardíacas difiere entre pacientes con delirium o delirium subsindromal y aquellos sin delirium, en estado de reposo (i.e.*resting state*) en condiciones de ojos abiertos y ojos cerrados.

En la secuencia de la tesis, este artículo representa el segundo nivel de análisis del cuerpo vivo, situándose como puente entre los parámetros autonómicos modificados descritos en el Artículo 1 y la vivencia subjetiva explorada en el Artículo 3. Esto permite preparar la transición hacia el estudio cualitativo del Artículo 3, orientado a comprender las experiencias corporales y cognitivas de los pacientes desde una perspectiva encarnada, mediante un enfoque constructivista de Teoría Fundamentada.

ARTÍCULO 3 — Bodily and Cognitive Experience in patients with sepsis and delirium or subsyndromal delirium (cuerpo vivido)

(Aceptado en Revista Nursing Critical Care, Q1)

1) Pregunta, objetivo y relación con la tesis

La pregunta que orienta este artículo es: ¿Cómo vivencian las personas que han experimentado delirium los cambios corporales y cognitivos durante el episodio? El objetivo es explorar y describir la experiencia del cuerpo vivido, identificando los significados atribuidos a los cambios corporales y cognitivos reportados por los participantes.

Este estudio constituye el nivel experiencial dentro del enfoque multinivel de la tesis. A través de un análisis cualitativo basado en Teoría Fundamentada constructivista, busca comprender cómo las personas articulan, interpretan y dan sentido a su experiencia corporal y cognitiva durante el delirium. Su contribución radica en complementar los hallazgos fisiológicos identificados en los Artículos 1 y 2, mostrando cómo el cuerpo vivido —manifestado en la percepción, la afectividad y la conciencia encarnada— se expresa en relación con los procesos del cuerpo vivo previamente descritos. De este modo, aporta una mirada fenomenológica que permite situar la fisiología en la experiencia encarnada de los pacientes.

2) Diseño y metodología, con justificación teórica y técnica

Se empleo Teoría Fundamentada (Grounded Theory). Este diseño permite generar categorías emergentes sobre percepciones corporales, experiencias sensoriales,

conciencia de sí, emociones y cambios cognitivos. La justificación teórica proviene del marco de la cognición corporeizada y de la distinción de Fuchs entre cuerpo vivo y cuerpo vivido. Dado que la experiencia consciente emerge de la circularidad causal —la influencia recursiva de la vivencia subjetiva sobre la regulación corporal—, la metodología cualitativa resulta pertinente para capturar esta dimensión desde la narrativa, las sensaciones y el significado atribuido por los propios pacientes. Este enfoque permite explorar cómo las experiencias corporales y cognitivas expresan, complementan o tensan los procesos fisiológicos descritos en los estudios anteriores.

3) Sinopsis del artículo y lugar en la secuencia de la tesis

Este artículo aborda el nivel experiencial, explorando cómo las personas que vivieron delirium o delirium subsindromal interpretan y significan los cambios corporales y cognitivos ocurridos durante la hospitalización por sepsis.

En el conjunto de la tesis, el Artículo 3 constituye el nivel final, centrado en el cuerpo vivido. Aunque no establece un vínculo causal directo con los hallazgos fisiológicos de los Artículos 1 y 2, sí analiza en profundidad las experiencias subjetivas de quienes atravesaron delirium o delirium subsindromal, incluidos en el estudio fisiológico. Con ello, complementa la evidencia previa al describir cómo los pacientes experimentan y narran sus cambios corporales y cognitivos en relación con la inestabilidad del cuerpo vivo. Este enfoque encarnado permite comprender el delirium no solo como una alteración fisiológica, sino como un fenómeno vivido que integra modificaciones en la percepción, el sentido del yo corporal, la orientación y la continuidad de la experiencia.

ARTICULO 1

Characterizing Autonomic Nervous System Alterations in Hospitalized Patients with Delirium: A Scoping Review

Characterizing Autonomic Nervous System Alterations in Hospitalized Patients with Delirium: A Scoping Review

Abstract

Purpose: To characterize autonomic nervous system alterations in patients with delirium, focusing on cardiovascular, respiratory, ocular, exocrine, and gastrointestinal functions, as well as neurotransmitter levels. This review aims to synthesize current evidence and explore potential clinical implications for monitoring delirium.

Methods: A scoping review was conducted in accordance with PRISMA-ScR guidelines and the Joanna Briggs Institute framework. Searches were performed on the Web of Science, PubMed, Scopus, and EBSCOhost. Eligible studies included experimental, quasi-experimental, observational, or descriptive designs involving hospitalized adults with delirium, diagnosed using standardized tools and accompanied by documented evaluation of the autonomic nervous system.

Results: Twenty-seven studies were included. Four domains were identified: cardiovascular activity (18 studies), which addressed heart rate variability, blood pressure variability, and blood flow. Several studies have reported changes in heart rate variability, increased blood pressure variability, and a reduction in mean arterial pressure associated with delirium. Four studies examined ocular changes, reporting reduced pupillary reflex responses in delirium. Gastrointestinal function was assessed in three studies through gut microbiota analysis, showing reduced microbial diversity and increased pathogenic taxa. Two studies examined neurotransmitter levels, reporting elevated norepinephrine in blood and urine associated with delirium.

Conclusions: This scoping review describes autonomic alterations reported in delirium across various domains, including cardiovascular, ocular, gastrointestinal, and neurochemical systems. Although these findings highlight the relevance of autonomic dysregulation in delirium, current evidence does not clarify the mechanisms linking autonomic changes to cognitive symptoms. Autonomic measures may indicate physiological vulnerability, but standardized and longitudinal studies are required to determine their prognostic value and clinical utility.

Keywords*:* Delirium, Autonomic Nervous Systems, Pupillary Reflex, Heart rate, Blood pressure, microbiota, norepinephrine

1. Introduction

Delirium is an acute disorder characterized by fluctuating cognitive impairment, including inattention and altered consciousness (American Psychiatric Association, 2013). It affects the sleep-wake cycle, emotional and psychomotor aspects (Maldonado, 2018), and is not associated with pre-existing neurocognitive conditions. The hospital prevalence is 23% (Gibb et al., 2020), varying according to medical unit and patient-related risk factors (E. S. Oh et al., 2017). The incidence ranges from 15% to 55.4% in internal medicine, predominantly affecting elderly patients (Inouye et al. 1993; Al Farsi et al., 2023), 10% in surgical units (Iamaroon et al., 2020), and 20% in non-cardiac surgeries (Abate et al., 2021). Rates exceed 50% in cardiac surgery with cardiopulmonary bypass (Rudolph et al., 2009) and reach 33-80% in intensive care units (ICU) (Wu et al., 2022).

Delirium arises from the interaction between predisposing factors, such as advanced age, dementia, functional decline, cardiovascular disease, and central nervous system (CNS) disorders, and precipitating factors including surgery, systemic illness, metabolic disturbances, medications, and environmental influences (Ormseth et al., 2023). At the neurobiological level, delirium has been associated with widespread disruptions in neurotransmitter balance and altered functional integration of brain networks. Functional magnetic resonance imaging (fMRI) studies report reduced network modularity, whereas electroencephalography (EEG) consistently demonstrates alpha slowing, suggesting a breakdown in large-scale neural communication (van Montfort et al., 2019). These central disturbances provide a framework for considering whether systems that link the CNS and peripheral physiology—such as the autonomic nervous system—may also be affected.

The nervous system comprises both central (CNS) and autonomic (ANS) components, with the latter integrated within the CNS through the Central Autonomic Network (CAN). This distributed network coordinates autonomic regulation processes by integrating interoceptive signals to generate adaptive responses required for homeostasis and allostasis (Shouman and Benarroch, 2021). The CAN encompasses cortical regions including the insula, cingulate,

and prefrontal cortices, as well as subcortical structures such as the amygdala, hypothalamus, thalamus, and brainstem autonomic nuclei (Ferraro et al., 2022; Sklerov et al., 2019). Functionally, it serves as the central integrative hub of the ANS, embedding autonomic control within the CNS and coordinating sympathetic and parasympathetic output.

This integration implies that autonomic regulation is embedded within neural systems involved in arousal and cognitive state regulation, processes that are broadly disrupted during delirium (Ferraro et al., 2022; Quadt et al., 2022). The peripheral ANS, through its sympathetic and parasympathetic branches, innervates major organs and relays viscerosensory information to the CAN while receiving descending autonomic commands that regulate cardiovascular, respiratory, gastrointestinal, pupillary, and sudomotor activity (Quigley et al., 2021; Candia-Rivera, 2022). Autonomic dysfunction observed in neurodegenerative diseases (Longardner et al., 2022) and age-related impairment (Mahinrad et al., 2016) further suggests that disturbances in ANS regulation may be associated with deficits in attention, awareness, and executive control (Forte et al., 2019). Lower heart rate variability (HRV) is one example of a peripheral autonomic measure linked to these processes. Peripheral autonomic measures, such as heart rate variability (HRV), have been associated with cognitive vulnerability in other clinical contexts (Forte et al., 2019). Given the role of the central autonomic network in integrating central and peripheral autonomic regulation, autonomic alterations may accompany the fluctuating course of delirium. However, existing evidence is limited and heterogeneous, highlighting the need for a scoping review to characterize reported autonomic changes and the methods used to assess them in patients with delirium.

2. Methods

2.1 Protocol

In this scoping review, the Joanna Briggs Institute (JBI) guidelines for scoping reviews (Peters et al., 2020) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping reviews (Tricco et al., 2018) were applied to the structure and development of the study. The

protocol was registered on the Open Science Framework on April 7, 2024 (https://osf.io/wez4g/).

2.2 Review questions and aims.

We aimed to identify gaps in the literature and to characterize alterations in ANS function in patients with delirium. The question was constructed using the PEO (Population, Exposure, Outcome) format (Hosseini et al., 2024): What specific changes in ANS activity have been identified in patients with delirium? A secondary question explored: What methods have been used to study alterations in ANS function? The review examines cardiovascular, respiratory, ocular, exocrine, gastrointestinal, plasma, and urinary neurotransmitter levels in patients with delirium. It also identifies clinical tools used to assess ANS activity.

2.3 Eligibility Criteria

Eligibility criteria were defined using the JBI framework (participants, concept, context, source types). Included studies were experimental, quasi-experimental, analytical observational, and descriptive observational designs. Participants were hospitalized adults (≥18 years) with a documented delirium assessment and ANS evaluation during hospitalization (Table 1). Studies published in English or Spanish with no date restrictions were included. Exclusion criteria involved studies without clear delirium records, qualitative research, opinion letters, and literature reviews.

Table 1. Areas and concepts for the search for the ANS

ANS area	Records and evaluations
Autonomic nervous system	Consider the sympathetic and parasympathetic autonomic nervous system.
Cardiovascular activity	Heart rate and variability (SDNN, SDANN, rMSDD, pNN50), ii) blood flow (tilt table testing), iii) blood pressure (Valsalva maneuver, isometric handgrip test, cold pressor test, baroreflex sensitivity testing), iv) orthostatism (active standing- blood pressure, head-up tilt test) (Zygmunt and Stanczyk, 2010; Freeman and Chapleau, 2013).
Respiratory activity	Changes in respiratory rate and deep breathing (deep breathing test) (Appenzeller et al., 2022)
Ocular changes	Changes in the pupil (pupillometry) and blinking (Pertab et al., 2018).

ANS area	Records and evaluations
Autonomic nervous system	Consider the sympathetic and parasympathetic autonomic nervous system.
Changes in exocrine glands	Changes in the skin are associated with sweating processes (sympathetic skin response or conductance) (Zygmunt and Stanczyk, 2010; Freeman and Chapleau, 2013).
Gastrointestinal changes	Changes in the gastrointestinal tract. Considering aspects of motility, emptying, and transit (esophageal manometry, gastroduodenal, anorectal, colonic; gastric, intestinal emptying scintigraphy, gastric emptying; microbiota) (Kornum et al., 2021)
Neurotransmitters in plasma or urine	Norepinephrine concentration (Zygmunt and Stanczyk, 2010)

2.4 Information Resources

Searches were conducted in the Web of Science, PubMed, SCOPUS, and EBSCOhost. The search strategy was reviewed by the team and refined by an ANS expert physician (A.G.). Refined results were exported to Google Sheets, where duplicates were removed.

2.5 Search

Search followed Peer Review of Electronic Search Strategies (PRESS) checklist (McGowan et al. 2016) and used Medical Subject Headings (MeSH) terms, combined with advanced free-text searching using keywords and Boolean operators (Supplementary Table 1). Generating the search syntax:

(delirium OR "Acute confusional state" OR "acute brain failure") AND ("autonomic nervous system" OR "parasympathetic nervous system" OR "sympathetic nervous system" OR "heart rate" OR "blood flow" OR "blood circulation" OR "tilt-table test" OR "blood pressure" OR "arterial pressure" OR "Valsalva Maneuver" OR "baroreflex" OR "orthostatic hypotension" OR "standing position" OR "respiratory rate" OR "pupillometry" OR "blinking" OR "sweating" OR "Galvanic Skin Response" OR "skin" OR "gastrointestinal transit" OR "Gastrointestinal Motility" OR "colonic" OR "scintigraphy" OR "microbiota" OR Norepinephrine).

Literature searches are presented as a PRISMA Flow Diagram (Figure 1).

2.6 Selection of Sources

The evidence selection process was documented in a Google Sheets-based database titled *"*Scoping Review ANS Delirium 2024*",* stored in the institution's secure Google Drive repository. This database contained separate tabs for search, eligibility, and final inclusion. Collected data included article ID, database, search syntax, authors, title, year, abstract, DOI, and search date.

a) Duplicate removal: Articles with duplicate titles and DOIs were removed.
b) Title and abstract screening (pilot phase): Three reviewers (E.A., M.R., V.C.) independently screened titles and abstracts, achieving a 90% agreement rate on eligibility criteria before advancing.
c) Title-Abstract Selection (Final Phase): Articles were independently screened and cross-reviewed to finalize selections for full-text review. A.G. and E.A. reviewed confusing articles, resolving disagreements through team discussion.
d) Full Article Selection: Four reviewers (E.A., M.R., V.C., R.O.) independently assessed full texts. Disagreements were resolved collaboratively. The included studies were compiled in a tab for analysis.

The selection process was reported and illustrated using the PRISMA-ScR flow diagram (Tricco et al. 2018).

2.7 Data charting process

Four investigators (E.A., M.R., V.C., R.O.) independently extracted data using a standardized and calibrated process and shared a common database. The calibration phase was completed before extraction, with each reviewer testing the process on a designated article. Independent pairs reviewed each article, and the results were verified with the team. Extracted data were summarized based on predefined categories aligned with the review's objectives. Discrepancies were resolved through team discussions.

The process followed a narrative synthesis approach (Arksey and O'Malley, 2005; Tricco et al., 2018), presenting the results in diagrams, graphs, and tables.

2.8 Data items

Data extraction focused on six ANS functions: cardiovascular, respiratory, ocular, exocrine gland, gastrointestinal, and neurotransmitter levels in plasma or

urine (Table 1). Analytical grouping was defined by reviewers (E.A., M.R., V.C., C.A., A.G., R.O.), and the research team resolved discrepancies.

The database recorded extracted data, considering study aims, design, country, language, medical unit, diagnoses, medical conditions, sociodemographic data, sample size, ANS-related outcomes, ANS dimensions, delirium, ANS assessment tools, and key findings. The data selection adhered to the CONSORT-Outcomes (Butcher et al., 2022), STROBE (Cuschieri, 2019), and SPIRIT (Chan et al., 2013) guidelines.

2.9 Critical Appraisal

The quality of the included studies was independently assessed by reviewers (E.A., M.R., V.C., R.O.) using JBI instruments (JBI 2017a, 2020, 2017b) tailored to each study type.

2.10 Synthesis

The included studies were summarized and grouped by the ANS functional domains. Data were organized into tables in Microsoft Word and complemented with figures for visual synthesis. Figures include only autonomic parameters reported in at least two studies to emphasize recurrent findings. All team members contributed to the synthesis process

3. Results

3.1 Selection of sources of evidence

A total of 3507 articles were identified. After title and abstract screening, 153 articles were assessed for full-text eligibility; finally, 27 articles were included (Figure 1). The characteristics of all included studies are presented in Table 2.

Figure 1. PRISMA 2020 flow diagram

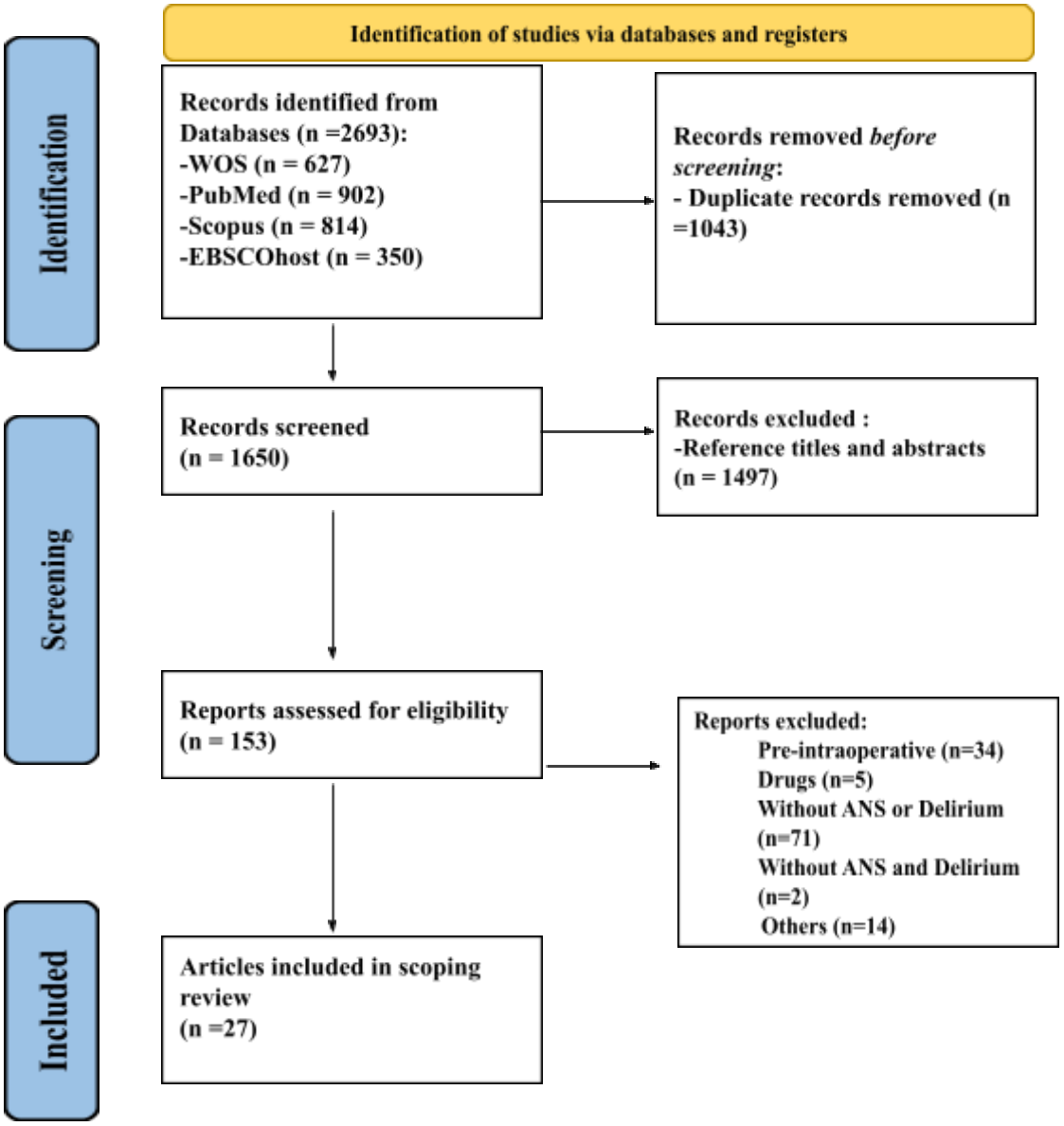


Table 2. Characterization of studies selected

Authors (Año)	Study Design	Medical Unit	Inclusion Criteria	Sample Size	Hospitalization Diagnosis n (%)	Female n(%)	Age mean (S.D.) or median [p25- p75]	Delirium n (%)	Delirium Assessment	Delirium Assessment Period
Cardiovascular										
Zorko et al., 2023	Retrospective cohort	ICU	Patients aged ≥18 years admitted to medical or surgical ICUs for at least 24 hours, with a minimum of 10 blood pressure measurements within the first 24 hours.	66549	Not reported	28234 (42.4%)	Entire sample 66 [54–77]	13427 (20.1%)	CAM-ICU RASS	Each 8 to 12 hours during stay in ICU (until 28 days)
Ooms et al., 2023	Not reported	ICU	Patients who underwent head and neck reconstruction with microvascular free flaps for malignant or non-malignant diseases	110	Radial forearm flap 48 (43.6%) Anterolateral thigh flap 50 (45.5%) Fibular flap 6 (5.5%) Iliac crest flap 2 (1.8%) Lower leg perforator flap 2 (1.8%) Latissimus flap 2 (1.8%)	41 (37.27%)	No POD 65.0 (20.0) POD 73.0 (16.0).	55 (50%)	CAM	Postoperative time extension is not declared
Tsukakoshi. et al., 2023	Retrospective cohort	Cardiac ICU	Patients aged ≥65 years who underwent open chest or abdominal, cardiovascular surgery and postoperative rehabilitation intervention.	79	Coronary artery bypass 12 (13,27%) Valvular 23 (24,27%) Thoracic aorta 31 (32,27%) Abdominal aorta 18 (19,27%) Combined 16 (17,27%)	25 (26.26%)	Event free 74.5 [70.7- 80.2] Combined events 77.0 [73.0- 81.0] *	31 (32.26%)	ICDSC	Once a day during stay in the ICU
Garbajs et al., 2022	Cohort	ICU	Participants aged ≥ 50 years enrolled in the MCSA and admitted to the ICU.	1130	Not reported	419 (37%)	Entire sample 84 [79–88]	185 (16.37%)	CAM-ICU RASS	Each 8 to 12 hours during the stay in the ICU
Rollo et al., 2022	Cross-sectional	Stroke unit	Adults ≥ 18 years with ischemic or hemorrhagic stroke, symptom onset within 72 hours, and NIHSS score ≥ 1 at first delirium assessment.	56	Left side stroke 26 (46.4%)	24 (42.8%)	Entire sample 69.9 (13.2)	11 (19.6%)	CAM-ICU RASS	First evaluation was performed at baseline, second register 72 h after admission, or whenever patients displayed symptoms of delirium
Shanahan et al., 2021	Prospective cohort	Geriatric	Using convenience sampling, participants aged ≥ 65 years were recruited as inpatients under a geriatric service.	29	Not reported	15 (51.7%)	Entire sample 80.8 (6.2)	17 (58.2%)	DRS-R DSM IV	No reported

Spiropoulou et al., 2022	Not reported	Surgical cardiac ICU	Patients aged > 65 years who underwent cardiac surgery with cardiopulmonary bypass, were extubated, had no known psychiatric disease, and were able to understand the language.	86	Heart valve 36 (41.9%) CABG 24 (27.9%) Combined 26 (30.2%)	29 (33.7%)	Samples are separated by age group <74 years: 48 (55.8%) ≥ 75 years: 38 (54.2%)	22 (25.6%)	CAM-ICU RASS DSM IV	Postoperative, but it was not described explicitly
Stokholm et al., 2021a	Prospective cohort	Stroke unit	Patients aged ≥ 18 years with an acute ischemic stroke diagnosis, including new neurological deficits lasting > 24 hours or confirmed ischemic lesions on CT/MRI.	64	Acute stroke	24 (34.4%)	Entire sample 70 (9.8)	8 (12.5%)	CAM	Daily on weekdays, a time extension is not declared
Sun et al., 2021	Prospective cohort	Not reported	Patients aged ≥ 60 years are scheduled for orthopedic surgeries (THA, TKA, RTKA, RTHA, hip fracture repair, and FSF surgery) under spinal anesthesia.	294	THA - RTHA 81 (27.55%) TKA - RTKA 158 (53.74%) Hip fracture repair 38 (12.92%) FSF 17 (5.78%)	218 (74.1%)	No POD 69.4 (7.43) POD 73.9 (8.11)	60 (20.4%)	3D- CAM DSM V DRS-R	One day before the scheduled surgery and daily up to the seventh postoperative day
Ernst et al., 2020	Not reported	Emergency	Patients with hip fractures and sinus rhythm confirmed via ECG in the emergency department.	54	Hip fracture	42 (77.7%)	Entire sample 83.5 (8.6)	37 (68.5%)	CAM	Preoperative and until the fifth postoperative day
Maheshwari et al., 2020	Retrospective Cohort	Surgical ICU	Patients admitted to the surgical ICU within 8 hours post-surgery and staying in critical care for at least 48 hours.	1083	Organ transplant 217 (20%) Digestive surgery 308 (28%) Musculoskeletal surgery 237 (22%) Other 321 (30%)	499 (46%)	Entire sample 62 (14)	377 (34.81%)	CAM-ICU RASS	Each 12 hours within 5 days after surgery during ICU hospitalization
Caldas et al., 2019	Prospective observational	ICU	Patients aged >18 years undergoing elective coronary artery bypass graft surgery with EuroSCORE ≥ 6 or LVEF ≤ 40%.	67	Cardiac Surgery (Bypass coronary)	16 (23.88%)	Entire sample 64.3 (9.5)	17 (25.37%)	CAM CAM-ICU	From post-procedure day 1 until discharge from the ICU
Neerland et al., 2019	Observational pilot	Geriatric	Patients aged ≥ 65 years acutely admitted with infections to the acute geriatric ward.	14	Respiratory Tract Infection 8 (57%) Urinary Tract Infection 4 (29%) Erysipelas 1 (7%) Cholecystitis 1 (7%)	7 (50%)	Entire sample 86 [74–91]	5 (35.7%)	CAM MDAS DSM V	Pre- and post-head-up tilt HUT
Sanson et al., 2019	Prospective longitudinal	Cardiac Unit	Adults aged > 17 years undergoing open-chest cardiac surgery with extracorporeal circulation and able to understand Italian.	199	CABG 102 (51.3%) Valvular surgery 53 (26.6%) Valvular/CABG surgery 24 (12.1%) Aortic surgery 20 (10.1%)	49 (24.6%)	Entire sample 67.9 (10.3)	61 (30.65%)	CAM-ICU ICDSC	Three times daily for up to five days in the PICU or upon discharge
Xie et al.,	Prospective	ICU	ICU patients with sepsis	112	Severity Sepsis 18 (16.1%)	35 (31.25%)	Entire sample 57.62	45 (40.2%)	CAM-ICU	Twice a day during the

2019	cohort		diagnosed using standard international criteria, including severe sepsis and septic shock		Severe sepsis 58 (51.8%) Septic shock 36 (32.1%)		(16.31)			stay in ICU time extension is not declared
Nguyen et al., 2018	Prospective cohort	ICU	ICU patients with shock were admitted to a 24-bed multidisciplinary department	252	Septic shock 114 (45%) Cardiogenic shock 100 (40) Hemorrhagic shock 38 (15)	84(33%)	Entire sample 68 (14)	185 (73%)	CAM-ICU RASS	Twice a day during the stay in ICU
Jooyoung et al., 2017	Not reported	ICU	Not reported	60	Not reported	23 (38.3%)	64.7 (15.9)	No reported	CAM-ICU RASS	Once a day, the time extension is not declared
Zaal et al., 2015	Prospective cohort	ICU	Patients aged 30–80 years admitted for more than 24 hours.	25	Respiratory failure 9 (36%) Hemorrhage 6 (24%) Trauma 3 (12%) Postoperative GI surgery 2 (8%) Infection, other 5 (20%)	7 (28%)	No delirium 57 (16) Delirium 67 (12)	13 (52%)	CAM-ICU DSM IV RASS	No reported
Ocular changes										
Okamoto et al., 2022	Prospective observational	ICU	Patients ≥18 years admitted to medical or surgical ICUs.	133	Not reported	46 (36.5%)	67.9 (12)	24 (18%)	ICDSC	During ICU stay, up to 7 days
Stokholm et al., 2021b	Prospective observational	Stroke unit	Patients aged ≥18 years with an acute ischemic stroke diagnosis, including new neurological deficits lasting >24 hours or confirmed ischemic lesions on CT/MRI.	64	Acute stroke 64 (100%)	22 (34.4%)	70 (9.8)	8 (12.5%)	CAM	Daily on weekdays, the time extension is not declared
Favre et al., 2020	Observational cohort	Surgical ICU	Critically ill medical-surgical patients requiring sedation and mechanical ventilation for ≥48 hours, with a high risk of ICU delirium	100	Infections/Sepsis 51 (51%) Cardiovascular 28 (28%) Chronic respiratory diseases 11 (11%) Gastrointestinal 6 (6%) Trauma 3 (3%)	67 (67%)	65 [53–74]	57 (57%)	CAM-ICU RASS	Twice a day during the stay in ICU
Yang et al., 2018	Prospective observational	PACU	Patients aged ≥18 years undergoing surgery during pre-, peri-, and postoperative periods.	47	General Surgery 10 (27%) Gynecological surgery 6 (16%) Orthopedic surgery 21 (57%)	14 (30%)	PACU- no delirium 49 [23–84] PACU-Delirium 65 [46–81]	10 (21.2)	CAM-ICU	15 and 60 minutes after admission
Gastrointestinal										
Garcez et al., 2023	Prospective study	Emergency	Patients aged ≥ 65 years hospitalized for less than 24 hours.	133	Cardiovascular 47 (35%) Sepsis/infection 33 (25%) Neurological 25 (19%) Others 28 (21%)	59 (44.4%)	75 (8)	38 (28.6%)	CAM 10-CS Attention test RASS	Twice daily throughout the hospital stay

Zhang et al., 2023	Prospective observational cohort study	Not reported	Patients aged ≥ 65 years scheduled for elective knee replacement, hip replacement, or laminectomy under general or spinal anesthesia	86	Knee replacement 53 (61,6 %) Hip replacement 26 (30,2%) Spinal stenosis 7 (8,1%)	46 (53.5%)	Delirium: 72.0 [70.5–75.3]; No delirium: 71.0 [69.0–76.8]	10 (14%)	CAM, MDAS	Postoperative days one and two
Yang et al., 2022	Prospective randomized single-center study	Not reported	Patients aged ≥ 65 years old with ASA grades I–III were diagnosed with early-stage gastric cancer and scheduled for elective radical gastrectomy.	81	Gastric cancer / Tumor stage: T1N0M0 27 (33,3%) T2N0M0 54 (66,6%)	34 (41.9%)	Preparation group 73 (5) Non preparation 74 (4)	17 (21.0%)	3D-CAM	Twice daily for 5 days successively after surgery
Neurotransmissors										
Deiner et al., 2014	Prospective cohort	Postoperative care unit or emergency	Patients aged > 68 years are scheduled for major non-cardiac surgeries requiring ≥ 2 days of hospital stay. Patients were contacted by phone at least 24 hours prior to surgery.	76	Spine 37 (48,68%) Urologic 9 (11,84%) General 22 (28,95%) Thoracic 8 (10,53%)	40 (52.63%)	76.33 (5.75) 73.48 (5.03).	14 (18.42%)	CAM MMSE	During the recovery room stay and on each postoperative day
Rigney, 2010	Observational	ICU	Participants aged ≥ 65 years in the ICU spoke and understood English.	44	Not declared	19 (43%)	75.7 (6.42)	13 (29%)	CAM	Evaluation was performed between 48 and 72 hours after admission.

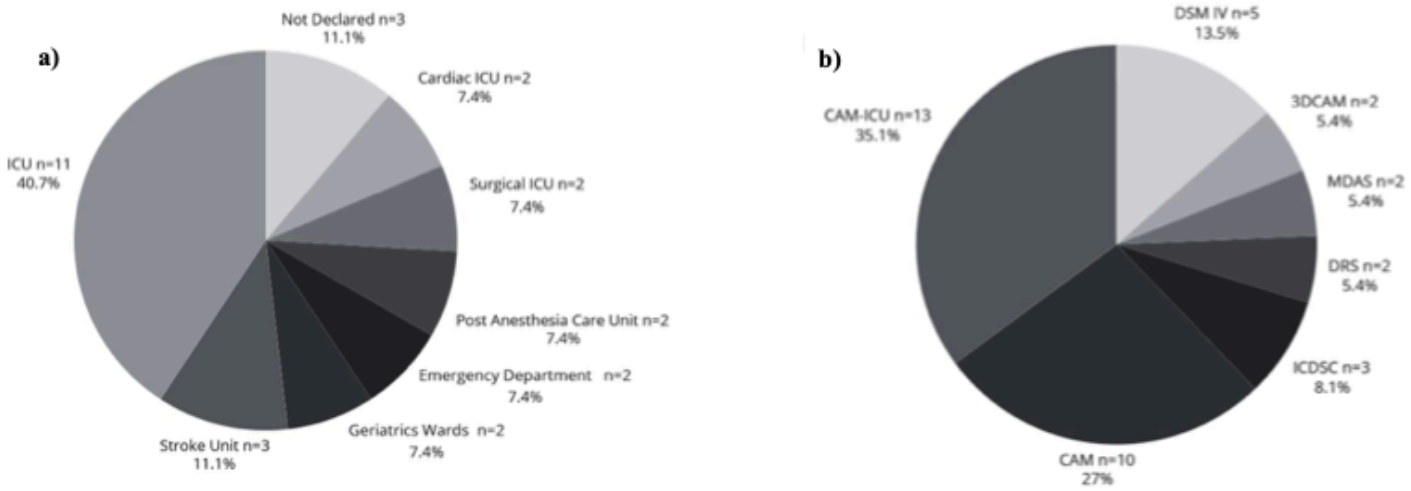
The studies were ordered by area of the autonomic nervous system identified, secondly by year of publication, and finally in alphabetical order.

*Combined event groups consider patients who die and are readmitted within 1 year of discharge. However, the study shows cardiac parameters comparing patients with delirium and those without delirium (**10-CS**) 10-point Cognitive Screener, (**3D-CAM**) 3-Minute Diagnostic Interview for Confusion Assessment Method–defined delirium, (**ASA**) American Society of Anesthesiologists, (**CABG**) Coronary Artery Bypass Grafting, (**CAM**) Confusion Assessment Method, (**CAM-ICU**) Confusion Assessment Method for the Intensive Care Unit, (**CT/MRI**) Computed Tomography / Magnetic Resonance Imaging, (**DMSS**) Delirium Motor Subtyping Scale, (**DRS-R**) Delirium Rating Scale–Revised, (**DSM**) Diagnostic and Statistical Manual of Mental Disorders, (**ECG**) Electrocardiogram, (**FSF**) Femoral Shaft Fracture, (**ICDSC**) Intensive Care Delirium Screening Checklist, (**ICU**) Intensive Care Unit, (**LVEF**) Left Ventricular Ejection Fraction, (**MCSA**) Mayo Clinic Study of Aging, (**MDAS**) Memorial Delirium Assessment Scale, (**NIHSS**) National Institutes of Health Stroke Scale, (**PACU-D**) Post-Anesthesia Care Unit Delirium, (**PICU**) Postoperative Intensive Care Unit, (**POD**) Postoperative Delirium, (**RASS**) Richmond Agitation–Sedation Scale, (**RTHA**) Revision Total Hip Arthroplasty, (**RTKA**) Revision Total Knee Arthroplasty, (**THA**) Total Hip Arthroplasty, (**TKA**) Total Knee Arthroplasty.

3.2 Characteristics of source evidence

The ANS functions identified were cardiovascular activity (n = 18) (Zorko Garbajs et al., 2023; Ooms et al., 2023; Tsukakoshi et al., 2023; Garbajs et al., 2022; Rollo et al., 2022; Shanahan et al., 2021; Spiropoulou et al., 2022; Stokholm, Ahmed, et al., 2021; Sun et al., 2021; Ernst et al., 2020; Maheshwari et al., 2020; Caldas et al., 2019; Neerland et al., 2019; Sanson et al., 2018; Xie et al., 2019; Nguyen et al., 2018; J. Oh et al., 2017; Zaal et al., 2015), ocular function (n = 4) (Okamoto et al., 2022; Stokholm, Birkmose, et al., 2021; Favre et al., 2020; Yang et al., 2018), gastrointestinal function (n = 3) (Garcez et al., 2023; Zhang et al., 2023; Yang et al., 2022), and neurotransmitters (n = 2) (Deiner et al., 2014; Rigney, 2010). Most studies were conducted in ICUs (n = 11, 47.7%), followed by stroke (n = 3, 11.1%), geriatrics (n = 2, 7.4%), emergency (n = 2, 7.4%), and other units (Figure 2). For delirium assessment (Table 2), the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was the most frequently used tool (n = 13, 35.1%). This was followed by the Confusion Assessment Method (CAM) (n = 10, 27%) and, less commonly, the Intensive Care Delirium Screening Checklist (ICDSC) (n = 3, 8.1%). Eight studies used more than two detection tools (Figure 2).

Figure 2. Characteristics of the studies.



a) Distribution of medical units of the studies entered, b) Distribution of delirium detection instruments

(3D-CAM) 3-Minute Diagnostic Interview for CAM-defined Delirium; **(CAM)** Confusion Assessment Method; **(CAM-ICU)** Confusion Assessment Method for the Intensive Care Unit; **(DSM-V)** Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; **(DRS)** Delirium Rating Scale; **(ICDSC)** Intensive Care Delirium Screening Checklist; **(ICU)** intensive care unit; **(MDAS)** Memorial Delirium Assessment Scale.

3.3 Critical Appraisal of sources of evidence

The quality of the included studies is shown in Table 3. All studies were included to provide an overview of current research, and findings should therefore be interpreted cautiously.

Table 3. Critical Appraisal of sources of evidence

JBI Critical Appraisal Checklist for Case Control Studies(JBI, 2017a)														
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10				TOTAL
Zorko et al. (2023)	Y	N	Y	Y	Y	U	Y	Y	U	Y				7/10
Garcez et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	U	Y				9/10
Ooms et al. (2023)	Y	Y	Y	U	Y	Y	N	Y	U	U				6/10
Tsukakoshi et al. (2023)	Y	N	Y	Y	Y	Y	Y	Y	U	Y				8/10
Zhang et al. (2023)	Y	N	Y	Y	Y	Y	N	Y	U	U				6/10
Garbajs et al. (2022)	Y	N	U	Y	Y	Y	Y	Y	Y	Y				8/10
Okamoto et al. (2022)	Y	N	Y	Y	Y	N	U	Y	U	Y				6/10
Spiropoulou et al. (2022)	Y	Y	Y	Y	Y	Y	Y	U	U	Y				8/10
Yang et al. (2018)	Y	N	Y	Y	Y	Y	Y	Y	N	Y				8/10
Shanahan et al. (2021)	Y	N	Y	Y	Y	Y	U	N	U	U				5/10
Sun, et al. (20219	Y	N	Y	Y	Y	Y	U	Y	Y	U				7/10
Stokholm et al. (2021a)	Y	N	Y	Y	Y	Y	Y	U	U	Y				7/10
Stokholm et al. (2021b)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y				9/10
Ernst et al. (2020)	Y	N	Y	Y	Y	Y	N	Y	U	N				6/10
Favre et al. (2020)	Y	N	Y	Y	Y	Y	U	Y	Y	U				7/10
Maheshwari et al. (2020)	Y	N	Y	Y	Y	Y	N	U	Y	U				6/10
Caldas et al. (2019)	Y	Y	Y	Y	Y	Y	Y	Y	U	Y				9/10
Neerland et al. (2019)	Y	N	Y	Y	Y	Y	U	Y	U	U				6/10
Xie et al. (2019)	U	Y	Y	Y	Y	Y	Y	Y	Y	Y				9/10
Nguyen et al. (2018)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y				9/10
Sanson et al. (2019)	Y	N	Y	Y	Y	Y	N	Y	N	U				6/10
Jooyoung et al. (2017)	U	N	Y	Y	Y	N	N	N	U	Y				4/10
Zaal et al. (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				10/10
Deiner et al. (2014)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y				9/10
Rigney et al. (2010)	U	U	Y	Y	Y	N	U	Y	Y	N				5/10
JBI Critical Appraisal Checklist for Randomized Controlled Trials(JBI, 2020)														
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	
Yang et al. (2022)	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	12/13
JBI Critical Appraisal Checklist for Cross Sectional(JBI, 2017b)														
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Rollo et al. (2022)	Y	Y	Y	Y	N	Y	Y	U	Y	U	U			7/11

Key: Y yes, N no, U unclear. * Quality analysis using Joanna Briggs Institute critical appraisal tools (Peters et al., 2020)

3.4 Results of individual sources of evidence

The four areas examined in this review are detailed in Table 4. As part of the synthesis, Figure 3 includes only the autonomic parameters reported in at least two studies, allowing the visualization of findings that are repeated in the literature. An overview of the ANS parameters measured is provided in Supplementary Table 2, which summarizes the definitions of the parameters assessed in the included studies. Each of the areas is described below.

Table 4. Findings of Autonomic Nervous System Changes in Patients with Delirium.

Authors	Measurement parameters	Equipment	Registration time of ANS	Analysis of the ANS performed	Findings associated with delirium during hospitalization
Cardiovascular					
Tsukakoshi et al. (2023)	HR	ECG (Bedside Monitor CSM-1000 series LifeScope from Nihon Kohden)	HRV was recorded for one hour during daytime and one hour during the nighttime, up to ICU discharge.	Temporal measure i) r-MSSD, SDNN Frequency measure ii) LF/HF Ratio, HF power	> RMSSD (day) > HF power (day) > LF/HF ratio (day, night)
Rollo et al. (2022)	HR	Bipolar chest lead ECG with a sampling rate of 512 Hz	ECG recordings were obtained at baseline within 24 hours of hospital admission.	Temporal measure i) Mean HR, STD, mean RR, SDNN, RMSSD, NN50, pNN50, triangular index, TINN, SD1, SD2 Frequency measure ii) PSD of LF and HF (Absolute power (ms), Relative power (%), normalized units (n.u.)), ratio LF/HF	> HR variability (STD) < HF nu
Sun et al. (2021)	HR	ECG was measured by a 12-lead Holter monitor (Biomedical Instruments Limited Company, Shenzhen, China)	HRV was recorded at the end of surgery and during the subsequent 24-hour postoperative period.	Temporal measure i) SDNN, SDNN index, RMSSD Frequency measure ii) HR, HF (n.u.), LF (n.u.), VLF (ms), ULF (ms), TP (total power)	< SDNNI < ULF POD was negatively correlated with SDNNI, VLF, ULF, and TP
Ernst et al. (2020)	HR	ECG was measured using a Biocom 4000, with dry silver/silver chloride electrodes attached to the right and left fingers	HRV was recorded during hospital admission prior to surgery, within 24 hours of arrival, using a 5-minute recording.	Temporal measure i) SDNN, RMSSD Frequency measure ii) TP, HF, LF, LF/HF ratio, total power (TP)	> SDNN > HF nu < LF nu
Oh et al. (2017)	HR	ECG, equipment not declared	In the ICU, recordings were obtained eight times over one day. Each sample was 7 minutes.	Temporal measure i) Mean HR, mean RR, SDNN, RMSSD Frequency measure ii) Absolute power HF, LF, HF (n.u), LF (n.u.), LF/HF	> SDNN > RMSSD
Zaal et al. (2015)	HR	Bipolar chest leads to ECG	Data were collected over two days at four time points during ICU stay, with each recording lasting 15 minutes.	Frequency measure i) Power of VLF (ms), LF (ms), HF (ms), HF (n.u.)	No differences were observed
Ooms et al. (2023)	BP	Intraoperative and postoperative blood pressure was measured using the IntelliVue X2 M3002A device (Philips), and postoperative values were recorded invasively or non-invasively with a blood pressure cuff.	SBP and MAP were recorded intraoperatively at 15-minute intervals and postoperatively at 5-minute intervals.	i) SBP deviations ii) MAP deviations	> SBP variability < minimum MAP

Zorko Garbajs et al. (2023)	BP	No declared blood pressure monitor	Blood pressure was recorded at intervals of 15 minutes to 1 hour during the first 24 hours of ICU stay.	Blood Pressure Variability measure i) SBP, DBP ii) ARV of BPV iii) Range iv) SD v) Maximum Δ	> SBP variability (ARV > 5 mmHg) > DBP variability
Garbajs et al. (2022)	BP	No declared blood pressure monitor	Blood pressure was measured at 15-minute to 1-hour intervals during the first 24 hours of ICU admission	Blood Pressure Variability measure i) SBP, DBP ii) ARV of BPV iii) Range iv) SD v) Maximum Δ vi) Residual SD	> SBP variability (ARV > 5 mmHg) > DBP variability
Shanahan et al. (2021)	BP	Orthostatic test, Beat-to-beat photoplethysmography with the Task Force® Monitor (CNSystems, Austria) during tilt table testing	Tilt-table testing was performed at least six weeks after delirium resolution.	Blood Pressure and Orthostatic Measure i) Orthostatic hypotension ii) Orthostatic hypertension	> SBP during tilt testing
Maheshwari et al. (2020)	BP	ICU blood pressure was measured with automated monitors and verified by nurses. Equipment details were not provided.	Intraoperative and postoperative period, up to five ICU days.	Hypotension MAP	< MAP (<75 mmHg)
Xie et al. (2019)	BP	BP was measured using the IntelliVue MP60 monitor (Philips, Netherlands) with a cuff fitted to the participant's arm	First 24 hours after admission. with hourly recordings.	MAP (SD)	> BPV
Sanson et al. (2018)	BP	No declared equipment	At admission and prior to delirium onset; timing not specified.	MAP	< MAP
Spiropoulou et al. (2022)	BP/HR	No declared	Pre-, intra-, and postoperative, timing not explicitly reported.	i) SBP y DBP iii) HR	< HR
Caldas et al. (2019)	BP/HR	Non-invasive BP was measured using the Finometer PRO (Finapres Medical Systems, Amsterdam, Netherlands) with a finger arterial volume clamp at T1 and T3. Invasive BP was measured using an arterial catheter connected to the Philips Monitor MP50 (Philips, Germany) at T2.	One day before surgery, one day after surgery, and seven days after surgery (5 minutes of registration)	i) Mean BP y BPV ii) HR	No differences in MAP or HR
Neerland et al. (2019)	BP/HR	Orthostatic tests were performed using a Task Force Monitor (TFM) (CNSystems Medizintechnik, Graz,	Morning assessment a few days after admission (duration of the recording included a 5-minute baseline in the supine position,	Blood pressure i) SBP, DBP, MAP, SI, CI, TPRI Temporal measure of HRV	> SDNN.

		Austria). Blood pressure was recorded using the Finapres finger plethysmography technique, electrocardiogram (ECG), and impedance cardiography (ICG) to record transthoracic impedance.	followed by a 10-minute tilt to 70 degrees)	ii) SDNN, pNN50, RMSSD Frequency measure of HRV iii) VLF, LF, HF nu, LF nu, LF/HF	
Nguyen et al. (2018)	BP/HR	BP was continuously monitored via a radial or femoral arterial catheter; HR was not declared. Equipment not declared	From ICU admission, with hourly recordings during ICU stay	Blood Pressure i) Highest/lowest values of DBP, MAP Heart Rate ii) HR	< MAP for 5 days < DBP for 5 days. DBP < 50 mmHg was associated with delirium Various episodes of MAP < 65 mmHg or MAP < 50 mmHg increase the risk of delirium
Stokholm et al. (2021a)	Blood flow	Facial temperature was measured using a FLIR T430sc infrared thermographic camera with a frontal view.	Twice daily during acute stroke ward (maximum of 3 hours)	Measure temperature facial in the following points: Supratrochlear (ST), Temporal (TEMP), Lateral palpebral commissure (LPC), iv) Medial palpebral commissure (MPC), v) Nasolabial (NL), vi) Labial commissure (LC), vii) Inferior labial (IL)	< Temperature MPC
Ocular changes					
Okamoto et al. (2022)	Pupillary constriction	Pupillary light reflex was measured using a NeurOptics PLR-200™ portable infrared pupillometer	Immediately after ICU admission.	AIP parameters extracted from pupillary light reflex: MAX, MIN, CH, LAT, CV, MCV, DV, NPi.	< DV
Stokholm et al. (2021b)	Pupillary constriction	PLRdil.vel. was measured using a portable infrared pupillometer (PLR-3000™, NeurOptics).	Twice daily on weekdays	DV, CV	< DV
Favre et al. (2020)	Pupillary Light Reflex	Automated infrared pupillometer (AlgiScan®, ID-Med)	Twice daily from 3 to day 7 of mechanical ventilation	Quantitative PLR, CV	< q-PLR day 3 with mechanical ventilation until day 7 < CV from day 3 with mechanical ventilation to day 5
Yang et al. (2018)	Pupillary constriction	Pupillary assessment was measured with a NeurOptics PLR-200™ portable infrared pupillometer	(i) After signing informed consent, (ii) 20 min after intubation, (iii) upon turning off primary maintenance inhaled anesthetic, (iv) 15 min, and (v) 45 min after PACU admittance, and (vi) at the time of PACU discharge.	Pupil diameter, MIN, CH, LAT, CV, T75	< CH < DV
Gastrointestinal					

Garcez et al. (2023)	Microbiota	Rectal Swab Samples microbiota evaluation	There are 3 moments: i) Admission ii) 72 hours after iii) During delirium onset or resolution	q2-diversity was employed to assess microbiota diversity and the abundance of bacterial taxa. Alpha diversity and Beta diversity. The core microbiota, defined as taxa detected in all samples (CORE 100%) or many samples within each group (CORE 75-80%)	< Microbial diversity (< Shannon and Pielou indexes) < *Lactobacillus* < *Peptoniphilus* > *Bacteroides* > *Enterococcus* *Serratia* was associated with the occurrence and severity of delirium *Bacteroides*, *Methanobrevibacter*, and *Varibaculum* were identified as CORE 80% in delirium episodes
Zhang et al. (2023)	Microbiota	Fecal swab sample collection	Postoperative period	The 16S rRNA gene sequencing was performed by BGI America (Cambridge, MA). The relative abundance in 16S rRNA sequencing refers to the proportion of a specific bacterial species or group of bacteria relative to the total number of bacterial sequences in each sample.	> Parabacteroides distasonis
Yang et al. (2022)	Microbiota	Fecal swab sample collection	There are 2 moments: i) Two days before surgery ii) Morning of surgery.	16S rDNA high-throughput sequencing was performed on fecal samples by Realbio Genomics Institute (Shanghai, China). Bacterial diversity was assessed by α-diversity (Chao 1) and β-diversity (principal coordinates analysis, PCoA). Linear discriminant analysis (LDA) and effect size (LefSe) analysis were used to search different taxa	> Abundance of genera Bacteroides, Mogibacterium, Campylobacter, Cloacibacillus, Clostridium XlVa, Peptostreptococcus, and Veillonella < Abundance of genus Pseudomonas, Collinsella, and Olsenella
Neurotransmissors					
Deiner et al. (2014)	Stress markers	Blood stress markers	There are 3 moments i) Preoperative ii) 4 h after postoperative started iii) 2 h after postoperative	Levels of cortisol, epinephrine and norepinephrine	> Norepinephrine. There were no differences in intraoperative levels of stress markers.
Rigney (2010)	Stress markers	Urinary test	12-hour overnight urine samples upon admission	Allostatic Load, primary mediators (urinary cortisol, norepinephrine and epinephrine, and serum DHEAS) and secondary mediators (WHR, systolic and diastolic BP, and serum glycosylated hemoglobin, HDL, and TC/HDL ratio).	> primary mediator's score

(**AIP**) Automated infrared pupillometry; (**ARV**) Average real variability; (**BP**) Blood pressure; (**BPV**) Blood pressure variability; (**CH**) Contraction rate of the pupil; (**CI**) Cardiac index; (**CV**) Mean contraction velocity of the pupil; (**CVP**) Central venous pressure; (**DBP**) Diastolic blood pressure; (**DBPV**) Diastolic blood pressure variability; (**DHEAS**) Dehydroepiandrosterone sulfate; (**DP**) Delirium patients; (**DV**) Mean dilation velocity of the pupil; (**HDL**) High-density lipoprotein; (**HF**) High frequency; (**HFnu**) HF in normalized units; (**HR**) Heart rate; (**LAT**) Latency of the pupil; (**LF**) Low frequency; (**LF/HF Ratio**) Low frequency to high frequency ratio; (**MAP**) Mean arterial blood pressure; (**MAX**) Maximum pupil diameter; (**MCV**) Maximum contraction velocity of the pupil; (**MIN**) Minimum pupil diameter; (**NN50**) Number of normal-to-normal intervals differing by more than 50 milliseconds; (**NPi**) Neurological pupil index; (**pNN50**) Percentage of successive intervals greater than 50 ms; (**PLR dil vel**) Pupillary light reflex (dilation velocity); (**PSD**) Power spectral density; (**r-MSSD**) Root mean square successive difference; (**SCL**) Skin conductance level; (**SD1**) Standard deviation of data perpendicular to the axis of line-of-identity in Poincaré plot; (**SD1/SD2**) Ratio between SD1 and SD2; (**SD2**) Standard deviation of data along the axis of line-of-identity in Poincaré plot; (**SDNN**) Standard deviation of NN intervals; (**SDNNI**) Standard deviation of Normal-to-Normal intervals in 5-min segments; (**SBP**) Systolic blood pressure; (**SI**) Beat-to-beat stroke index; (**STD**) Standard deviation; (**TINN**) Triangular interpolation of NN; (**TP**) Total power; (**TPRI**) Total peripheral resistance index; (**T75**) Pupil recovery time to 75%; (**TWA**) Time-weighted average; (**ULF**) Ultra low frequency; (**VLF**) Very low frequency; (**WHR**) Waist–hip ratio.

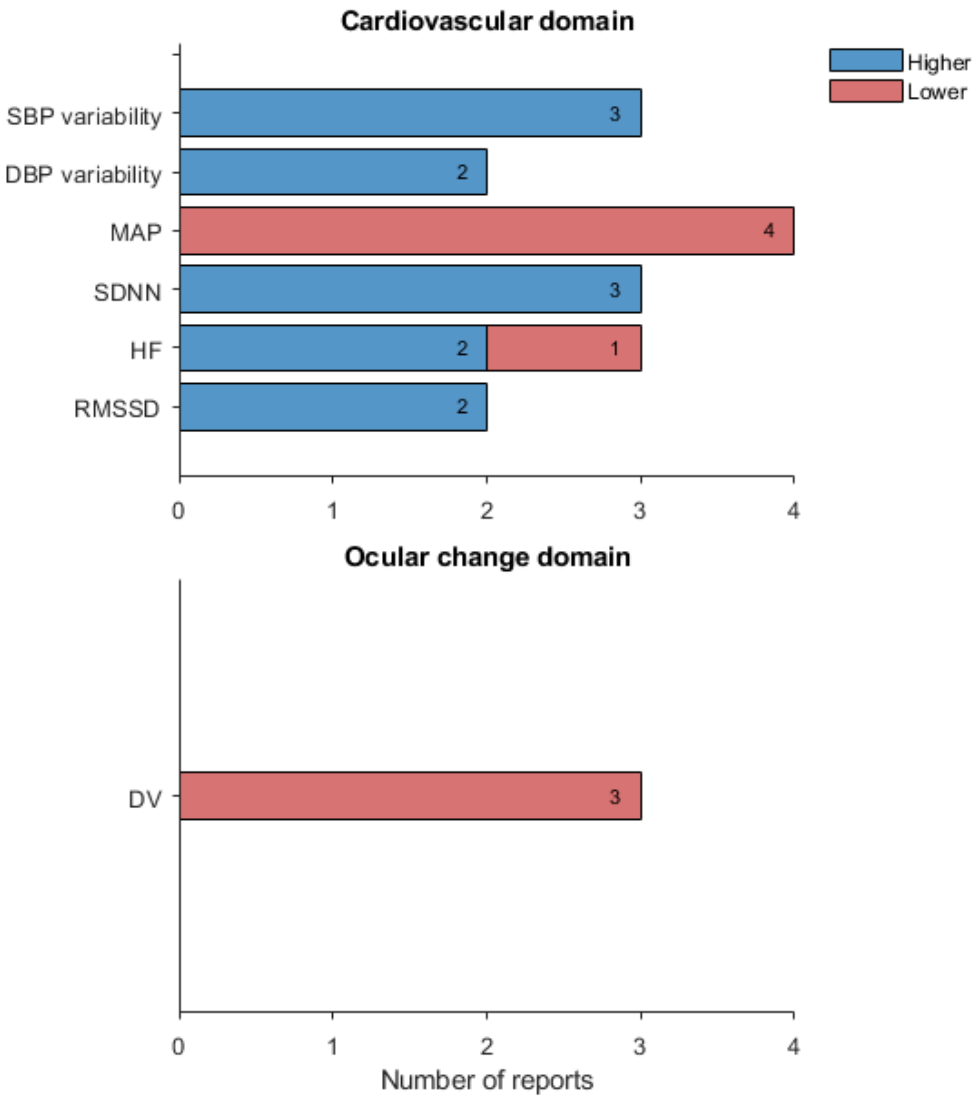


Figure 3. Recurrent autonomic parameters reported in patients with delirium. The y-axis displays autonomous parameters reported in at least two included studies, and the x-axis indicates the number of studies that report each parameter. Bars represent whether parameters were reported as higher (blue) or lower (red) in patients with delirium compared with patients without delirium, as described in the original publications. This figure provides a descriptive synthesis and does not reflect effect size, physiological magnitude, or causal relationships.

(**SBP variability**) systolic blood pressure variability; (**DBP variability**) diastolic blood pressure variability; (**MAP**) mean arterial pressure; (**SDNN**) standard deviation of normal-to-normal RR intervals; (**HF**) high-frequency power of heart rate variability; (**RMSSD**) root mean square of successive differences between RR intervals; (**DV**) pupillary dilation velocity.

Cardiovascular

Among the 18 studies included, ANS assessment methods comprised the following: heart rate variability (HRV) (n = 6), blood pressure variability (BPV) (n = 7), blood flow (BF) (n = 1), and combined HR and BP measures (n = 4) (Table 4).

HRV: All six HRV studies utilized ECG monitors. Recording durations varied; some studies measured within the first 24 hours (Rollo et al., 2022; Sun et al., 2021; Ernst et al., 2020), Zaal et al. (2015) recorded for two days at four different moments, (J. Oh et al., 2017) performed eight measurements in a day, and Tsukakoshi et al. (2023) recorded during the ICU stay until discharge.

Time-domain HRV analysis, including standard deviation of NN intervals (SDNN) and root mean square of successive differences (rMSSD) (Tsukakoshi et al., 2023; Rollo et al., 2022; Sun et al., 2021; Ernst et al., 2020; J. Oh et al., 2017). Additional indices comprised mean HR, mean RR intervals (J. Oh et al., 2017), and SDNN index (Sun et al., 2021), and extended time-domain parameters, including number of NN intervals differing by more than 50 ms (NN50), percentage NN50 (pNN50), triangular index, triangular interpolation of NN interval histogram (TINN), SD1, and SD2 (Rollo et al., 2022) (Supplementary Table 2). The main findings indicated higher rMSSD values in delirium patients (Tsukakoshi et al., 2023; J. Oh et al., 2017), as well as higher SDNN (Ernst et al., 2020; J. Oh et al., 2017) (Figure 3).

Frequency-domain HRV analysis was performed in all studies. Five studies assessed absolute power with normalized power units (Rollo et al., 2022; Sun et al., 2021; Ernst et al., 2020; J. Oh et al., 2017; Zaal et al., 2015). Low-frequency to high-frequency ratio (LF/HF ratio) was analyzed in four studies (Tsukakoshi et al., 2023; Rollo et al., 2022; Ernst et al., 2020; J. Oh et al., 2017); very low frequency (VLF) and ultra-low frequency (ULF) bands were also reported (Sun et al., 2021; Zaal et al., 2015). Findings for HF power were heterogeneous. Increased HF power was reported in Tsukakoshi et al. (2023) and Ernst et al. (2020), whereas reduced levels were observed in Rollo et al. (2022), and remained unchanged in J. Oh et al. (2017) and Zaal et al. (2015) LF/HF ratio increased in Tsukakoshi et al. (2023).

BPV: Seven studies were analyzed. Heterogeneous monitoring methods were reported, ranging from combined invasive /noninvasive (Ooms et al., 2023; Xie et al., 2019), photoplethysmography during an orthostatic (Shanahan et al., 2021), and unspecified techniques (Zorko Garbajs et al., 2023; Garbajs et al., 2022; Sanson et al., 2018; Maheshwari et al., 2020), within the first 24 hours of hospitalization (Garbajs et al., 2022; Zorko Garbajs et al., 2023; Xie et al., 2019), postoperative (Ooms et al., 2023), hourly for up to 5 days (Maheshwari et al., 2020), or after delirium onset (Shanahan et al., 2021).

Analysis focused on mean arterial pressure (MAP), systolic/diastolic BP with BPV indices (Zorko Garbajs et al., 2023; Garbajs et al., 2022; Ooms et al., 2023; Maheshwari et al., 2020; Xie et al., 2019; Sanson et al., 2018), or beat-to-beat and orthostatic changes (Shanahan et al., 2021). Lower MAP was consistently associated with delirium (Ooms et al., 2023; Maheshwari et al., 2020; Sanson et al., 2018; Nguyen et al., 2018), with risk thresholds reported at < 75 mmHg (Maheshwari et al., 2020) and at < 50 mmHg or repeated MAP < 65 mmHg (Nguyen et al., 2018). In addition, increased systolic and diastolic BPV was reported in patients with delirium (Ooms et al., 2023; Zorko Garbajs et al., 2023; Garbajs et al., 2022)(Figure 3).

BP/HR: Four studies were conducted for this analysis. Monitoring methods ranged from combined invasive and non-invasive approaches (Caldas et al., 2019) to finger plethysmography, electrocardiography, and impedance cardiography (Neerland et al., 2019), however, two studies did not specify the techniques used (Spiropoulou et al., 2022; Nguyen et al., 2018).

Recording periods varied, including postoperative days 1-7 (Caldas et al., 2019), hourly ICU measurements (Nguyen et al., 2018), or multiple days of geriatric monitoring (Neerland et al., 2019). Analysis included mean MAP, systolic BP (SBP), diastolic BP (DBP), and HR variability (Spiropoulou et al., 2022; Caldas et al., 2019; Neerland et al., 2019; Nguyen et al., 2018). Lower MAP thresholds and hypotensive episodes were consistently associated with delirium (Maheshwari et al., 2020; Nguyen et al., 2018), while higher resting-state SDNN was reported in geriatric patients (Neerland et al., 2019).

Blood flow: Only one study, conducted by Stokholm, Ahmed et al. (2021), assessed facial temperature using an infrared camera twice daily during the

patient's stay in the stroke unit. The study reported a decrease in temperature at the medial palpebral commissure in delirium patients.

3.4.1 Ocular changes

Four studies examined the pupillary reflex using different devices: NeurOptics PLR-200™ (Okamoto et al., 2022; Yang et al., 2018), PLR-3000™ (Stokholm, Birkmose, et al., 2021), and AlgiScan R, ID-Med (Favre et al., 2020). Measurement schedules varied, including assessments at ICU admission (Okamoto et al., 2022), twice daily in a stroke unit (Stokholm, Birkmose, et al., 2021), twice daily from day 3 to 7 mechanical ventilation (Favre et al., 2020), and post-anesthesia care unit (PACU) admission to discharge (Yang et al., 2018).

Quantitative pupillary metrics included maximum (MAX) and minimum (MIN) pupil diameters, contraction velocity (CV), pupil contraction rate (CH), contraction latency (LAT), mean and peak contraction velocity (MCV), time to 75% recovery (T75), dilation velocity (DV), neurological pupil index (NPi), quantitative pupillary light reflex (q-PLR). All studies reported pupillary impairments in patients with delirium. Pupil DV was consistently lower in delirium patients (Okamoto et al., 2022; Yang et al., 2018; Stokholm, Birkmose, et al., 2021)(Figure 3). Meanwhile, q-PLR, CV, and CH were reduced (Favre et al., 2020; Yang et al., 2018).

3.4.2 Gastrointestinal

Three studies examining gut microbiota using fecal samples were reviewed. Garcez et al. (2023) used rectal swabs, storing samples at -20°C before transfer to -80°C. Zhang et al. (2023) obtained fecal swabs after post-orthopedic surgery; however, they did not provide details regarding the storage conditions. Yang et al. (2022) stored samples at -80°C, with and without mechanical bowel preparation.

Sampling timelines varied across studies: Garcez (2023) collected samples at baseline, 72 hours later, and upon changes in delirium status. Zhang et al.(2023) sampled only postoperatively, collecting samples two days before and on the morning of surgery.

Findings linked alterations in gut microbiota to delirium. Garcez et al. (2023) reported a reduction in microbial diversity, a decrease in the abundance of Lactobacillus and Peptoniphilus genes, and increased levels of Bacteroides

and Enterococcus. Zhang et al. (2023) found an increase in Parabacteroides distasonis in patients with postoperative delirium. Yang et al. (2022) identified a significant increase in Bacteroides and Veillonella following mechanical bowel preparation, suggesting a potential role for these bacteria in the development of postoperative delirium. Meanwhile, delirium patients had fewer Pseudomonas, Collinsella, and Olsenella species.

3.4.3 Neurotransmitters

Two studies examined neurotransmitter-related changes and stress markers in relation to the risk of delirium. Deiner (2014) measured blood cortisol, epinephrine, and norepinephrine at three time points: preoperatively, four hours after surgical initiation, and two hours postoperatively. Levels were compared between patients receiving total intravenous anesthesia (TIVA) and inhalational anesthesia (sevoflurane), finding that elevated postoperative norepinephrine increased delirium risk by 20% per 100 pg/mL increment. Rigney (2010) analyzed primary mediators, including urinary cortisol, norepinephrine, epinephrine, and serum DHEAS, alongside secondary outcomes such as waist-to-hip ratio, BP, glycosylated hemoglobin, HDL cholesterol, and TC/HDL ratio. Higher primary mediator scores were associated with a higher risk of delirium.

4. Discussion

This scoping review identified multiple autonomic alterations in patients with delirium, including changes in cardiovascular activity, ocular function, gastrointestinal function, and neurotransmitter levels. These findings indicate that autonomic variability commonly co-occurs with delirium. However, current evidence does not establish whether these alterations represent contributing mechanisms or parallel physiological responses to acute illness.

The heterogeneity of the included studies substantially limits the interpretation of findings. Differences in measurement devices, sampling frequency, recording duration, analytical algorithms, population characteristics, comorbidities profiles, underlying etiologies, medication exposure, delirium assessment tools, and the timing of autonomic measurements likely contributed to divergent findings. Taken together, these methodological and clinical inconsistencies

preclude the identification of a single autonomic profile that is consistently associated with delirium.

4.1 Cardiovascular Activity

HRV indices, including time-domain metrics such as rMSSD and SDNN, as well as the HF component in frequency-domain analyses, were evaluated across studies. Overall, these metrics showed heterogeneous patterns in delirium: some ICU, geriatric, and emergency cohorts reported higher rMSSD (Tsukakoshi et al., 2023; J. Oh et al., 2017)**,** HF (Tsukakoshi et al., 2023; Ernst et al., 2020), or SDNN (Neerland et al., 2019; J. Oh et al., 2017; Ernst et al., 2020) values in patients with delirium, whereas postoperative and stroke-related cohorts did not observe such increases (Sun et al., 2021; Rollo et al., 2022)**.** rMSSD and HF, derived from short-term R–R interval recordings, primarily reflect vagally mediated respiratory sinus arrhythmia and baroreflex related influences on sinoatrial node activity (Quigley et al., 2021; Shaffer and Ginsberg, 2017)**,** while SDNN represents global HRV shaped by multiple autonomic inputs and recording duration (Alcantara et al., 2020)**.** Although these mechanisms describe the physiological basis of HRV metrics, they do not identify specific autonomic processes underlying changes in delirium. In acutely ill hospitalized populations, rMSSD and SDNN are strongly influenced by systemic stress and clinical context (de Castilho et al., 2018), and overall HRV findings in delirium appear heterogeneous and context-dependent rather than reflecting a delirium-specific autonomic signature.

BPV, including systolic and diastolic components, presented greater variability in patients with delirium across medical and surgical ICUs (Ooms et al., 2023; Zorko Garbajs et al., 2023; Garbajs et al., 2022; Xie et al., 2019). Higher SBP responses were also observed during tilt testing in patients with delirium (Shanahan et al., 2021). Evidence from critical care populations indicates that elevated beat-to-beat BP fluctuations are associated with impaired dynamic cerebral autoregulation and intermittent changes in cerebral perfusion (Stulberg et al., 2023; Liu et al., 2024). Although these mechanisms have not been directly examined in delirium, they provide a physiological context for understanding how increased BPV may coexist with cognitive fluctuations, without implying a causal pathway.

MAP, the average arterial pressure across the cardiac cycle, is regulated by autonomic baroreflex adjustments (DeMers and Wachs 2019). A decrease in MAP was a recurring finding across the included studies (Maheshwari et al., 2020; Ooms et al., 2023; Sanson et al., 2018; Nguyen et al., 2018), and some studies reported associations with delirium (Maheshwari et al., 2020; Nguyen et al., 2018). External evidence suggests that MAP values below the lower limit of cerebral autoregulation are associated with reductions in cerebral blood flow, indicating that the vulnerability linked to low MAP in acute illness may be due to constraints in perfusion capacity (Kho et al., 2025). Taken together, BPV and MAP findings suggest that hemodynamic variability co-occurs with the fluctuating cognitive profile of delirium, although the underlying mechanistic pathways remain undetermined.

4.2 Pupillary Changes

Pupil size reflects a balance between sympathetic (dilation) and parasympathetic (constriction) activity (Gray et al., 2024; Wilhelm and Wilhelm, 2003). Constriction occurs when retinal input activates the pretectal nucleus and Edinger-Westphal (EW) nuclei, leading to parasympathetic innervation of the iris sphincter. Dilation is followed by inhibition of parasympathetic output at the EW nuclei and activation of sympathetic pathways that stimulate the iris dilator muscle via the α1-adrenergic signaling (Hall and Chilcott 2018).

Across the included studies, delirium was consistently associated with reductions in pupillary contraction (Favre et al., 2020; Yang et al., 2018) and dilation velocities (Okamoto et al., 2022; Yang et al., 2018; Stokholm, Birkmose, et al., 2021) Pupillary control depends on an integrated network comprising brainstem nuclei regulating arousal and attention, along with cortical and subcortical regions—including the insula, frontal eye fields, prefrontal cortex, superior colliculus, and locus coeruleus—that modulate responses during cognitive and emotional processing (Peinkhofer et al., 2019). This organization helps explain why pupillary dynamics are sensitive to changes in arousal and cognitive load; however, the alterations observed in this review should be interpreted as physiological correlates of delirium rather than evidence of specific neurotransmitter-based mechanisms, as none of the included studies directly assessed these pathways.

4.3 Neurotransmitters

Two studies reported that elevated peripherally measured norepinephrine levels in blood and urine were associated with an increased risk of delirium (Deiner et al., 2014; Rigney, 2010). Norepinephrine plays a central role in arousal and stress responses; however, the included studies did not examine central noradrenergic pathways, locus coeruleus activity, or motor subtypes of delirium. As such, these associations should be interpreted as peripheral physiological findings rather than mechanistic evidence.

In the broader delirium literature, two neurochemical frameworks are frequently referenced—the cholinergic deficiency hypothesis (Hshieh et al., 2008; Field et al., 2012) and the noradrenergic dysregulation hypothesis, which involves altered locus coeruleus activity (Hansen and Rediske, 2021; Wilson et al., 2020). These models aim to explain attentional impairment and symptom fluctuation in delirium but were not evaluated in the studies included in this review and therefore cannot be confirmed or contrasted.

4.4 Gut Microbiota

Reduced gut microbial diversity has been reported in patients with delirium, characterized by decreases in *Lactobacillus* and *Peptoniphilus* and increases in *Bacteroides* and *Enterococcus* (Yang et al., 2022; Garcez et al., 2023; Zhang et al., 2023). Through the gut–brain axis, microbiota can influence autonomic ANS activity (Cryan et al., 2019). Gut dysbiosis has been associated with systemic inflammation and increases cytokines such as IL-6 and TNF-α (Wei et al., 2022), mechanisms implicated in delirium.

However, only the loss of overall microbial diversity has been directly associated with altered ANS activity (Bonaz et al., 2018). Associations between certain bacterial taxa and increased inflammation or poorer cognitive outcomes have been described in other clinical contexts (Saji et al., 2019; Sugita et al., 2023), but their relevance to delirium or ANS function remains unclear (Saji et al., 2019; Sugita et al., 2023). These changes have not been shown to modify ANS activity. Overall, current findings suggest a connection between gut dysbiosis, systemic inflammation, and delirium, but the pathways linking microbiota alterations to autonomic changes remain undetermined. The available evidence is correlational rather than mechanistic, underscoring the need for studies that integrate microbiota profiles with inflammatory and autonomic measures.

4.5 Clinical Implications: Integrating Autonomic-Central Mechanisms in Delirium

The autonomic alterations identified in this review—particularly increased BPV, reduced MAP, and changes in pupillary dynamics—suggest that delirium is accompanied by instability across multiple physiological systems rather than a uniform shift in sympathetic or parasympathetic activity. This pattern is consistent with contemporary models that conceptualize delirium as a disorder of disrupted regulatory integration, in which fluctuating cognition arises alongside variability in neurophysiological, autonomic, vascular, and inflammatory control (Maldonado, 2018; Wilson et al., 2020). The heterogeneity of HRV findings reinforces that no single autonomic marker captures the multifaceted physiological instability characteristic of this condition.

Clinically, these findings underscore the potential value of multimodal autonomic assessment—integrating HRV, BPV, MAP, and pupillary dynamics—rather than reliance on isolated parameters to identify physiological vulnerability. They also highlight important methodological gaps, including variations in recording protocols, limited simultaneous monitoring of autonomic domains, and the absence of central autonomic measures, all of which restrict mechanistic interpretation (Maldonado, 2018; Fick et al., 2017; McKay et al., 2023). Future studies integrating neurophysiological, immunological, autonomic, and behavioral data may help clarify the relationship between physiological instability and the neurocognitive features of delirium.

4.6 Limitations

This review is limited by heterogeneity in study designs, autonomic assessment methods, and study populations. Differences in recording duration, analytical approaches, and the timing of autonomic measurements relative to delirium assessment limit the comparability of results across studies. Autonomic measures varied in terms of device type, sampling frequency, and analytical algorithms, while patient populations differed in age, comorbidities, illness severity, and exposure to medications that affect autonomic function. Variability in delirium assessment tools and their timing adds complexity. Overall, heterogeneity in autonomic outcomes reflects methodological and clinical variability rather than a single autonomic profile associated with delirium.

5. Conclusions

This scoping review shows that autonomic alterations commonly accompany delirium, affecting cardiovascular measures, pupillary responses, gastrointestinal function, and peripheral neurotransmitter levels. While these findings underscore the relevance of autonomic dysregulation in this condition, current evidence does not clarify the mechanisms linking autonomic changes to cognitive symptoms. Autonomic markers, such as HRV, BPV, MAP, pupillary dynamics, norepinephrine, and gut microbiota measures, may help identify physiological vulnerability. However, standardized protocols and longitudinal studies are needed to determine their prognostic value and their relationship to delirium.

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While preparing this work, the authors used Grammarly for language editing and ChatGPT to assist in creating the graphical abstract. The authors took responsibility for the final content. After using this tool, the authors reviewed the content as needed and took full responsibility for the content of the published article.

CRediT authorship contribution statement

E. A. conceived the study and was responsible for the study idea, design, methodology, implementation, analysis, and writing. C.A-R. contributed to the design, methodology, analysis, and writing. M.R., V.C., A.I.J.G., R.O.E., F.J.P., and G.C. contributed to the method, implementation, analysis, and writing. All authors read and approved the final manuscript.

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ARTÍCULO 2

HEARTBEAT-EVOKED POTENTIALS IN SEPSIS-ASSOCIATED DELIRIUM:

EXPLORING HEART–BRAIN INTEGRATION

HEARTBEAT-EVOKED POTENTIALS IN SEPSIS-ASSOCIATED DELIRIUM: EXPLORING HEART–BRAIN INTEGRATION

ABSTRACT

Background: Delirium is a common complication of sepsis and involves systemic inflammation, changes in autonomic regulation, and disturbances in brain network integration. The Heartbeat-Evoked Potential (HEP), a cortical response time-locked to the cardiac cycle, offers a means to examine cardiac–cortical coupling but has not been investigated in sepsis-associated delirium (SAD).

Objective: To characterize HEPs in septic patients with SAD, subsyndromal delirium (SSD) versus without delirium, and to assess their modulation across eyes-open (EO) and eyes-closed (EC) states. A secondary objective examined autonomic function using heart-rate variability (HRV).

Methods: Twenty adults with sepsis underwent EEG–ECG recording within 72 hours of admission. EEG was preprocessed using standardized artifact-reduction procedures, and HEP epochs were extracted by time-locking the signal to cardiac R-peaks using a −200 to 500 ms window. Data-driven non-parametric cluster statistics identified early and late HEP components. HRV indices were computed separately for EO and EC. Clinical, cognitive, HRV, and electrophysiological variables were compared across groups.

Results: No main effects of Group or State were observed for overall HEP amplitude. However, a significant Group × State interaction indicated differences in EO–EC modulation in patients with SAD/SSD. HRV indices were broadly similar across groups, except for a reduced LF/HF ratio during EO in delirium. Patients with SAD/SSD showed lower cognitive performance at discharge, particularly in global MoCA scores, attention, and abstraction.

Conclusions: Septic patients with SAD/SSD showed differences in state-dependent HEP modulation, while HRV measures were comparable between groups. HEP recording is feasible at the bedside in acute sepsis.

Keywords: Delirium, Heart evoked potential, Intensive care unit .

INTRODUCTION

Sepsis arises from a dysregulated host immune response to infection, resulting in systemic inflammation, multiorgan dysfunction, and a high mortality rate. Its pathophysiology involves complex inflammatory, metabolic, and neural interactions that make clinical progression unpredictable [1]. Globally, sepsis causes about 48.9 million cases and 11 million deaths annually[2].

Among the most frequent neurological complications is sepsis-associated delirium (SAD), a fluctuating disturbance of attention and cognition that affects up to 50% of critically ill patients[3], and is associated with higher mortality, longer hospitalizations, and persistent cognitive decline[5,6] . Subsyndromal delirium (SSD), an incomplete form of the syndrome, can occur in up to 70% of patients and has been associated with adverse clinical outcomes[4].

It is essential to acknowledge that delirium is not solely a neurological disturbance, but also involves pronounced physiological alterations, including alterations in autonomic regulation, fluctuations in arousal, motor disorganization, sleep–wake cycle fragmentation, and cardiovascular instability. In sepsis, the pathophysiology underlying these disturbances is multifactorial, encompassing neuroinflammation, endothelial and metabolic dysfunction, oxidative stress, and impaired microcirculatory flow [5,6]. This generates bodily shifts that exert a continuous influence on central nervous system function, potentially influencing large-scale cortical networks.

Despite this, most electroencephalography (EEG) studies in delirium have remained predominantly brain-centric. Traditional resting-state analyses have focused on cortical signal properties—such as increased delta and theta activity, reduced alpha power, decreased functional connectivity, and diminished signal complexity [7–10],

prioritizing cortical signal features and not routinely incorporating the bodily rhythms known to influence neural dynamics. This perspective overlooks the continuous influence of visceral signals that modulate cortical activity. Cardiac oscillations are known to couple with spontaneous brain dynamics, affecting the temporal organization of resting-state networks and contributing to variability in cortical activity [11,12].

The Heartbeat-Evoked Potential (HEP) is an event-related potential time-locked to the R-wave of the ECG that provides a direct measure of how cardiac activity is represented at the cortical level. The HEP has been used as a non-invasive measure of cardiac-related cortical activity, capturing the influence of cardiac afferent signals on ongoing neural dynamics[13–15]. Directing attention toward internal bodily cues significantly increases HEP amplitude compared with focusing on external stimuli, indicating that attentional shifts modulate HEPs. This effect is consistent across healthy individuals and clinical populations[16–20].

Experimental and clinical research shows that HEP amplitude varies with cardiovascular dynamics[21,22], arousal and consciousness fluctuations[13,23], stress[24], and pain[25], indicating that the cortical representation of the heartbeat is modulated by changes in the bodily environment[16–20] . Altered HEPs have been observed across a range of neurological and psychiatric conditions, where differences in cardiac–cortical coupling reflect changes in the way bodily information is integrated into brain activity[18,26–30]. Taken together, these findings position the HEP as a physiologically grounded marker for probing how systemic physiological disturbances influence cortical processing and for examining the coordination between bodily states and brain activity.

The present study aimed to characterize heartbeat-evoked potentials (HEPs) in septic patients with SAD or SSD, and in those without delirium, during acute hospitalization. The primary objective was to compare HEP amplitude across groups, while secondary objectives examined heart-rate variability (HRV) parameters and potential group differences during eyes-open and eyes-closed resting-state conditions.

METHODS

Study design.

A prospective observational study was designed using the STROBE guide[31]. Records were implemented during hospitalization, from admission to hospital discharge.

Research context.

This study was conducted at the Hospital Clínico de la Universidad de Chile in patients admitted to the Emergency Service or Critical Care Unit and was approved by the Hospital Clínico de la Universidad de Chile's ethics committee with number 71.

Participants

Patients were recruited between April and December 2023. These patients presented with renal, abdominal, and respiratory sepsis, defined by SEPSIS-3[32], and met the criteria.

Eligibility criteria.

i. Inclusion criteria: Clinical diagnosis of renal, abdominal, or respiratory sepsis, over 18 years of age, patient in the emergency room or ICU (in the latter unit, there may

be up to a maximum of 36 hours of hospitalization), and presence of informed consent (by the patient or related family member).

ii. Exclusion criteria: Diagnosis of Covid-19, history of chronic liver damage, cardiovascular instability that limits the performance of studies, defined as the presence of norepinephrine> 0.3 ug /kg/min (i.e., severe septic shock) despite initial resuscitation, need for emergency orotracheal intubation, previous cognitive impairment (by family report and AD8 instrument >2) and early adaptation in therapeutic life support measures, patient in end of life.

Informed consent was obtained from patients without delirium (Confusion Assessment Method for the ICU [CAM-ICU] = 0) or from legal representatives when CAM-ICU ≥ 1. All procedures were conducted in accordance with the Declaration of Helsinki.

Data collection

The following clinical, demographic, cognitive, and neurophysiological data were systematically collected for each participant:

a. Sociodemographic and clinical data: Age, education, sex, reason for admission, comorbidities (Charlson index), SOFA, APACHE II (Classification System for Chronic Diseases and Acute Physiology).
b. EEG/ECG acquisition: One evaluation per patient within the first three days of hospitalization.
c. Clinical data during EEG: Sedation agitation scale (SAS)[33] and delirium assessment with CAM-ICU[34]. Delirium is diagnosed if: (i) acute onset or fluctuating course and (ii) inattention, plus either (iii) disorganized thinking, or (iv) altered level of consciousness. A positive diagnosis requires both features (i) and (ii), and either (iii) or (iv). SSD is identified when some, but not all, of

these features are present. For analytic purposes, patients with SAD or SSD were classified as delirium-positive (D+), and those without delirium as delirium-negative (D−).

d. Cognitive assessment at discharge: Montreal Cognitive Assessment (MoCA, total and domain scores)[35] and Frontal Assessment Battery (FAB)[36], evaluating abstraction, verbal fluency, motor programming, interference sensitivity, cognitive flexibility, and inhibitory control.

EEG/ECG Acquisition

EEG was acquired with the Biosemi ActiveTwo system (16 active Ag/AgCl electrodes positioned according to the international 10-20 system). Signals were digitized at a sampling rate of 2048 Hz. Two additional electrodes (CMS/DRL) were used to create a reference feedback loop, replacing the traditional ground electrode. These signals were recorded after informed consent. The resting state was recorded under two conditions: i) with their eyes open (EO) for 5 minutes, where they looked at a red cross of 20 x 20 centimeters, physically located in front of the bed; and ii) with eyes closed (EC) for 3 minutes.

EEG processing

Offline EEG data processing was conducted using functions from both EEGLAB and FieldTrip toolboxes in the MATLAB environment [37], following:

1. High-pass filter at 0.01 Hz and a low-pass filter at 100 Hz.
2. Automatic bad channel detection (based on high variance, flat line, or artifact correlation) and spherical spline interpolation.
3. Line noise removal using the Zapline algorithm[38], followed by PREP pipeline[39]
4. Artifact Subspace Reconstruction (ASR) was applied to remove high-amplitude non-neural artifacts [40].

5. Final artifact reduction was achieved using Adaptive Mixture Independent Component Analysis (AMICA), while component classification was guided by ICLabel[41].

Cardiac activity (ECG) and Heart Rate Variability (HRV)

ECG was recorded simultaneously using two external bipolar channels. After resampling, R-peaks were detected on a 3–30 Hz filtered ECG using adaptive thresholding with semi-automated verification, based on functions from the HEPLAB toolbox [42] . Ectopic beats and artifacts were removed prior to HRV computation.

Time-domain HRV indices included the standard deviation of NN intervals (SDNN), root mean square of successive differences (RMSSD), and pNN50. Frequency-domain indices included low-frequency (LF: 0.04–0.15 Hz), high-frequency (HF: 0.15–0.30 Hz), and the LF/HF ratio.

Heart-Evoked Potential (HEP) analysis

Heartbeat-evoked potentials (HEPs) were analyzed using a 2 × 2 mixed-design with Group (D+ vs. D-) as the between-subjects factor and State (eyes open [EO] vs. eyes closed [EC]) as the within-subjects factor. For each participant, two condition-specific HEP waveforms were available (EO/EC) at all scalp channels and across a standard time base. Data were stored in a MATLAB structure containing all relevant data matrices per participant. All HEP analyses were implemented using MATLAB (R2024b).

HEP epochs were time-locked to the R-peak (t = 0 ms) and baseline-corrected using a -200 to 500 ms. For statistical analysis, we used the subject-level average HEP time series per condition, channel, and subject. We tested main effects using a

non-parametric mass-univariate framework across channels and time with temporal clustering within each channel [43].

Main effects and interactions were tested by adapting the pointwise statistic and permutation scheme to each factor. i) The Group main effect was assessed using a two-sample *t* statistic applied to each participant's state-averaged HEP, with group-label permutations (2500 permutations). ii) The State main effect was evaluated using a paired *t* statistic on the within-subject EO–EC difference, with sign-flip permutations (2500 permutations). iii) The Group × State interaction was tested using a two-sample *t* statistic on the within-subject EO–EC difference, again employing group-label permutations (2500 permutations)

Given the small number of sensors, we did not use spatiotemporal clusters based on channel adjacency (i.e., nearest-neighbour topology). Thus, samples exceeding a two-sided cluster-forming threshold ($\alpha = 0.05$, uncorrected) were grouped into temporal clusters using temporal contiguity (i.e., consecutive suprathreshold time points). For each temporal cluster, we summed the pointwise t-statistics (i.e., absolute mass, maximum absolute cluster mass across time). The family-wise error rate was controlled at $\alpha = 0.05$ using the permutation-based max-cluster method. We report significant clusters, including their temporal span, channel membership, p-value, raw difference of means (Δ mean), and robust effect size (Hedges' g with small-sample correction and 20% trimmed means). For visualization, 95% confidence intervals were obtained by permutations with resamples on trimmed means (1000 permutations). This analysis yields the data-driven interaction topographies and windows shown in the upper panels of Figure 1.

Sociodemographic, Clinical, and HRV Analyses

Statistical analyses for ECG metrics, sociodemographic, and clinical variables were performed using JASP (version 0.18.3) and GraphPad Prism 10.

Group differences in sociodemographic and clinical variables were examined first. Continuous variables were compared using independent-samples *t*-tests or Mann–Whitney *U* tests, depending on distribution (Shapiro–Wilk test), and categorical variables using χ^2 tests or Fisher's exact tests when appropriate.

For the HRV analysis, indices were computed separately for eyes-open (EO) and eyes-closed (EC) segments. Time-domain measures (SDNN, RMSSD, pNN50) and frequency-domain measures (LF, HF, LF/HF in absolute and normalized units) were compared between groups using the same approach: *t*-tests or Mann–Whitney *U* tests based on distributional assumptions.

RESULTS

Sociodemographic results

Twenty patients with sepsis were included (D− = 10; D+ = 10). Groups did not differ significantly in age, sex, years of education, comorbidity burden, or illness severity scores (Table 1). A trend towards lower Glasgow Coma Scale scores at admission was observed in the D+ group, although this difference was not statistically significant (all $p > 0.05$). Regarding delirium expression, D+ patients displayed heterogeneous CAM-ICU profiles, ranging from 2 to 4 diagnostic features. In contrast, apparent differences were observed in cognitive performance at discharge: D+ patients exhibited significantly lower global MoCA scores (D−: 22.6 ± 3.95 vs D+: 16.4 ± 3.27; $p = 0.018$, Hedges' $g = 1.86$), with pronounced impairments in the attention subdomain (D−: 4.9 ± 0.99 vs D+: 2.4 ± 0.70; $p = 0.009$, $g = 2.79$) and a

moderate deficit in abstraction (p = 0.048). FAB scores did not differ significantly between groups.

Table 1. Sociodemographic and clinical information

Variables	D-	D+	P-VALUE	Effect Size
Demographics				
Age	61.5 (14.16)	65.3 (12.91)	0.762	-0.268
Women	5 (50%)	7 (70%)	0.398	0.200
Scholarity	13.3 (4.37)	11.00 (3.49)	0.329	0.556
Clinical Status				
Fragility	2.1 (0.7)	2.1 (1.1)	0.937	0.030
Charlson	3.3 (2.11)	3.5 (2.1)	0.831	-0.093
SOFA	2.4 (0.69)	3 (1.05)	0.167	-0.340
Glasgow	14.9 (0.316)	13.9 (1.10)	0.06	0.540
SAS	3.9 (0.31)	3.5 (0.52)	0.064	0.400
PCR	175.670 (96.429)	267.460 (114.350)	0.068	-0.500
Days hospitalization	8.1 (4.5)	12.2 (6.32)	0.108	-0.430
Delirium characterization (CAM-ICU)				
2 symptoms		2 (60%)		
3 symptoms		2 (20%)		
4 symptoms		1 (10%)		
Cognitive test				
FAB	14.8 (2.530)	12.5 (3.659)	0.119	0.700
Total MOCA	22.6 (3.950)	16.4 (3.273)	0.018*	1.861
Visuoespacial	3.9 (0.876)	2.7 (1.337)	0.108	1.017
Attention	4.9 (0.994)	2.4 (0.699)	0.009**	2.785
Abstraction	1.3 (0.675)	0.4 (0.516)	0.048*	0.660

Confusion Assessment Method for the Intensive Care Unit (CAM-ICU); C-reactive protein (CRP); D- (without delirium); D+ (with sepsis-associated Delirium or subsyndromal delirium); Frontal Assessment Battery (FAB); Montreal Cognitive Assessment (MoCA); Sedation–Agitation Scale (SAS); Sequential Organ Failure Assessment (SOFA).

Heart Rate Variability (HRV)

HRV analyses included 19 participants (D− = 9; D+ = 10), as one participant from the D− group was excluded due to misplacement of electrodes during ECG signal acquisition.

Eyes open (EO). HRV indices did not differ significantly between groups across time-domain or frequency-domain parameters (all p > 0.05), except for the LF/HF ratio, which was lower in D+ patients (D−: 0.894 ± 0.358 vs D+: 0.640 ± 0.190; p = 0.039, g = 0.78).

Table 2. Heart Rate Variability parameters during the eyes-open condition

Variables	D-	D+	p-value	Effect Size
HRV Parameters				
Number of beats	349.333 (75.477)	357.600 (56.602)	0,842	-0.119
Mean intervals (ms)	839.159 (128.943)	685.864 (115.875)	0,0607	1.198
Min intervals (ms)	566.000 (94.726)	522.2000 (32.530)	0,4602	0.378
Max intervals (ms)	1399.778 (323.128)	1249.400 (286.417)	0,6259	0.472
Mean HR (bpm)	72.821 (9.735)	89.685 (14.660)	0,0607	-1.280
Min HR (bpm)	45.131 (11.727)	50.206 (10.675)	0,6259	-0.433
Max (ms)	108.157 (14.538)	115.259 (6.436)	0,4602	-0.616
SDNN (ms)	108.157 (14.538)	115.259 (6.436)	0,6457	0.244
RMSSD (ms)	98.751 (63.299)	96.666 (47.711)	0,842	0.067
pNN50	10.852 (11.661)	10.274 (6.745)	0,6457	-0.222
HF power (ms2)	$2.306x10^{+9}$ ($2.608x10^{+9}$)	$2.348x10^{+9}$ ($2.224x10^{+9}$)	0,842	0.067
LF power (ms2)	$1.661x10^{+9}$ ($1.628x10^{+9}$)	$1.443x10^{+9}$ ($1.329x10^{+9}$)	0,6461	0.200
LF/HF ratio	0.894 (0.358)	0.640 (0.190)	0,039*	0.778

bpm (beats per minute); HF (high-frequency power); HR (heart rate); LF (low-frequency power); LF/HF (ratio of low- to high-frequency power); pNN50 (percentage of successive NN intervals differing by >50 ms); RMSSD (root mean square of successive differences); SDNN (standard deviation of NN intervals).

Eyes closed (EC). No significant between-group differences were observed across any HRV indices during EC (all p > 0.05).

Table 3. HRV **parameters during the eyes-closed condition**

Variables	D-	D+	P-VALUE	Effect size
HRV Parameters				
Number of beats	222.444 (53.247)	246.667 (57.752)	0.959	-0.415
Mean intervals (ms)	851.067 (129.190)	696.161 (113.761)	0.104	1.212
Min intervals (ms)	614.444 (81.999)	563.778 (60.708)	0.575	0.0669
Max intervals (ms)	1278.444 (475.221)	1215.778 (349.813)	0.968	0.143
Mean HR (bpm)	71.812 (9.775)	89.285 (14.636)	0.104	-1.260
Min HR (bpm)	51.963 (16.507)	53.507 (17.028)	0.968	-0.089
Max (ms)	99.264 (13.665)	107.451 (10.764)	0.575	-0.634
SDNN (ms)	65.868 (45.858)	65.007 (43.544)	0.968	0.018
RMSSD (ms)	86.246 (70.793)	88.905 (67.666)	0.968	-0.038
pNN50	10.852 (8.715)	8.960 (8.215)	0.968	0.194
HF power (ms2)	$2.545x10^{+9}$ ($4.286x10^{+9}$)	$2.755x10^{+9}$ ($2.962x10^{+9}$)	0.968	-0.062
LF power (ms2)	$2.735x10^{+9}$ ($5.728x10^{+9}$)	$2.800x10^{+9}$ ($2.329x10^{+9}$)	0.968	-0.136
LF/HF ratio	0.957 (0.290)	1.233 (1.023)	0.968	0.062

bpm (beats per minute); HF (high-frequency power); HR (heart rate); LF (low-frequency power); LF/HF (ratio of low- to high-frequency power); pNN50 (percentage of successive NN intervals differing by >50 ms); RMSSD (root mean square of successive differences); SDNN (standard deviation of NN intervals).

Heart-Evoked Potentials (HEP)

Significant group differences were observed in the state-dependent modulation of HEPs across early posterior and later frontocentral time windows. In the early posterior window at Oz (120–176 ms; $p < 0.01$), both groups showed higher HEP amplitudes during the eyes-closed (EC) condition compared with eyes-open (EO). However, the magnitude of this modulation differed between groups: the D+ group exhibited more negative EO–EC values than the D− group, indicating a larger EC-related increase in HEP amplitude in patients with delirium or subsyndromal delirium.

In the later frontocentral window at Fz (290–316 ms; $p = 0.05$), the EO–EC difference was also larger in the D+ group than in the D− group, indicating greater state-dependent modulation of cardiac-related cortical activity in this group.

Figure 1 illustrates the grand-average HEP waveforms for EO and EC conditions, along with the EO–EC differential amplitudes used in the statistical analyses.

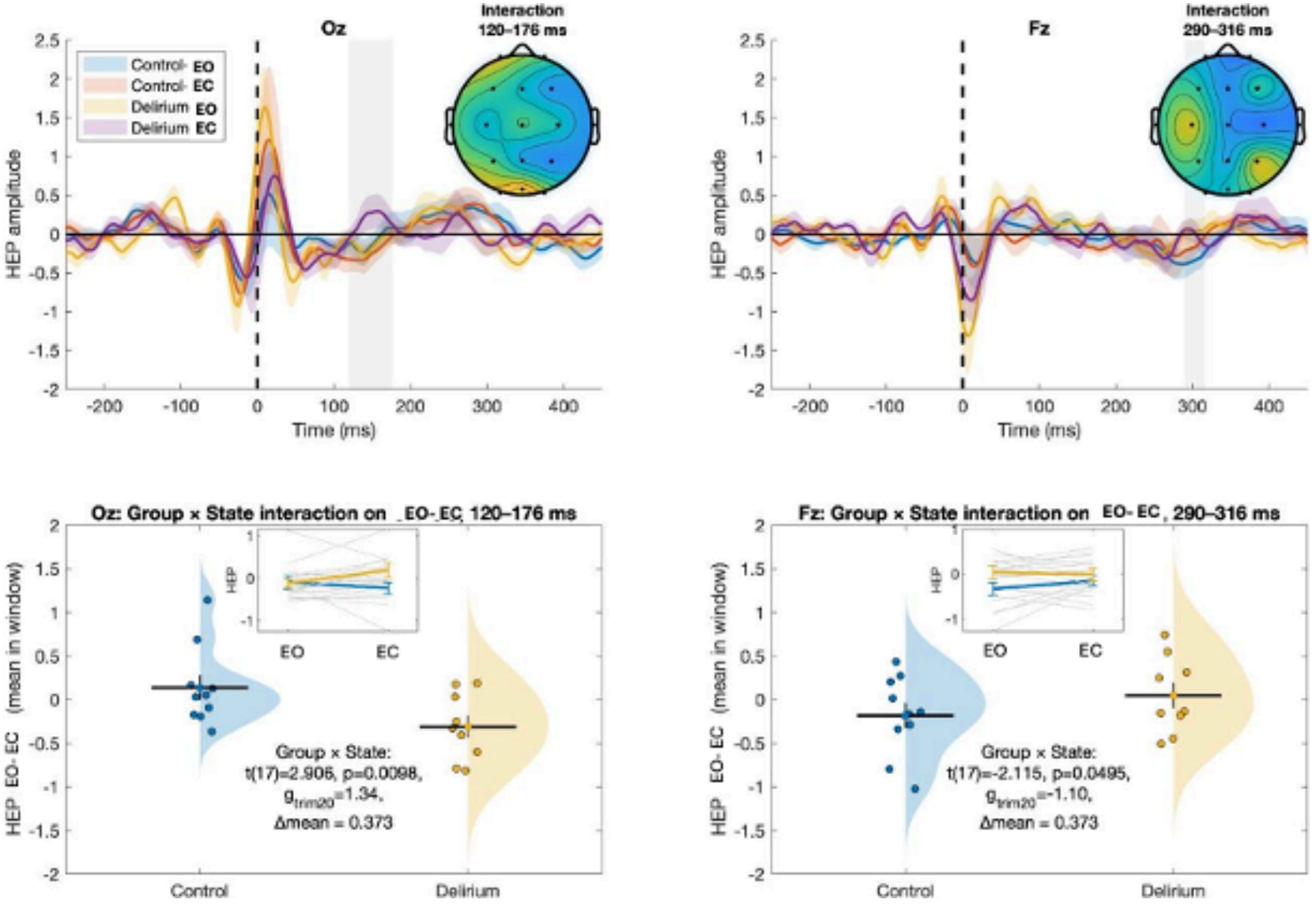

Figure 1. Heartbeat-evoked potentials (HEP) during eyes-open and eyes-closed conditions. The upper panels display the grand-average HEP waveforms for eyes-open (EO) and eyes-closed (EC) conditions at Oz and Fz for each group. The lower panels show raincloud plots of the EO–EC difference, which was the metric used for statistical testing of state-dependent modulation. Inset plots summarize the mean HEP amplitude within each significant time window for EO and EC separately, providing a descriptive view of absolute amplitudes per condition

DISCUSSION

The main findings emerged in line with the study objectives. First, no main effects of Group or State were observed on overall HEP amplitude across the analyzed time windows. Second, a significant Group × State interaction indicated that HEP amplitude changed differentially between EO and EC across groups. Third, HRV indices were broadly comparable between groups, except for a modest reduction in LF/HF during EO in the D+ group. Finally, patients in the SAD/SSD (D+) group demonstrated lower cognitive performance at discharge, particularly in global scores, attention, and abstraction.

State-dependent HEP modulation and delirium

The central neurophysiological finding was a significant Group × State interaction, indicating that state-dependent modulation of HEPs differed between eyes-open (EO) and eyes-closed (EC) conditions across groups. In the present study, both groups showed an EC-related increase in HEP amplitude in the early posterior window at Oz, consistent with previous findings in healthy adults reporting higher HEP amplitudes during EC compared with EO under resting-state conditions, likely reflecting reduced visual input[20,28]. This pattern indicates that HEPs were reliably detectable in septic patients and that state-dependent modulation was preserved in both groups.

However, the magnitude of the EO–EC difference at Oz differed between patients with SAD/SSD and controls, accounting for the observed Group × State interaction rather than differences in overall HEP amplitude.

Differences in EO–EC modulation were also observed in a later frontocentral window at Fz. Late HEP components have previously been linked to higher-order cortical

processing[14,44]. However, their functional significance in the context of acute critical illness remains uncertain. Given the fluctuating nature of attention and arousal in delirium [45,46], these differences may reflect variability in state-dependent cortical responses.

Taken together, these findings suggest that SAD and SSD are associated with differences in the modulation of cardiac-related cortical activity across resting-state conditions. Given the exploratory nature of the study, the modest sample size, and the limited spatial resolution of the EEG montage, these results should be interpreted as preliminary observations describing state-dependent neural responses to changes in sensory context rather than evidence of specific physiological deficits or mechanistic alterations.

HEP vs. HRV: relative contributions of central and peripheral physiology

HRV analyses showed that the delirium and control groups had broadly similar autonomic indices, with no between-group differences in standard time-domain or frequency-domain measures. The only exception was a lower LF/HF ratio during EO in the delirium group, an isolated finding that did not replicate in EC and should be interpreted cautiously given the debated physiological meaning of LF/HF and its instability in short recordings [47].

When compared with normative adult values for short-term HRV (SDNN ~40–70 ms; RMSSD ~20–50 ms) [48], both SDNN and RMSSD were higher in our sample. These values fall within the broad physiological heterogeneity described in sepsis, where HRV can appear reduced, preserved, or elevated depending on illness severity, timing of assessment, respiratory variability, and physiological instability[49,50].

Overall, the lack of robust HRV alterations and the presence of state-dependent HEP differences indicate that HEP alterations cannot be explained by autonomic indices

alone. Because HEP–HRV coupling was not assessed, central–peripheral interactions cannot be determined. In this cohort, cortical modulation differences were more prominent than autonomic ones.

Implications for understanding sepsis-associated delirium

Delirium involves instability in attention, fluctuating arousal, and disrupted processing of internal and external information [45,46]. In this context, the state-dependent HEP differences observed in this study indicate that cardiac-related cortical activity varies across sensory conditions (eyes open vs. eyes closed) in patients with delirium and subsyndromal delirium. These findings are best interpreted as reflecting variability in state-dependent cortical responses during acute sepsis among patients with delirium and subsyndromal delirium [46,51].

Lower cognitive performance at discharge in the delirium group aligns with evidence that both delirium and subsyndromal delirium are associated with short- and long-term cognitive impairment [4,52,53]. While the present data do not allow causal inferences, this finding underscores the clinical relevance of studying state-dependent neural dynamics during acute sepsis.

Despite substantial methodological challenges associated with electrophysiological recordings in critically ill patients—including arousal fluctuations, medication effects, environmental noise, and limited experimental control[54]—HEP morphology in this cohort reproduced canonical early and late components and the expected EC > EO pattern [14,18,20]. This demonstrates the feasibility of acquiring HEPs at the bedside and supports their potential utility for studying heart–brain interactions in acute illness.

Limitations

Several limitations must be acknowledged. The modest sample size limits statistical power and results in wider uncertainty around the effect size estimates [55]. Medication use, illness severity, and arousal fluctuations—known to influence EEG and autonomic physiology [49,50]—could not be fully controlled. HRV recordings were brief, limiting interpretability and comparability across studies[47]. Interoception was not assessed behaviorally, precluding direct linkage between HEP modulation and perceptual accuracy [11,20,56]. Methodologically, temporal clustering with a sparse EEG montage limits spatial inference, and ROI/time-window analyses serve as descriptive rather than confirmatory evidence[43]. Finally, robust effect sizes should be interpreted cautiously due to the uncertainty inherent in the sample size.

CONCLUSIONS

Septic patients with SAD/SSD showed differences in state-dependent modulation of the HEP across early posterior and later frontocentral time windows, while HRV measures were comparable between groups. These findings indicate that group-related differences were observed at the level of cortical responses time-locked to cardiac activity rather than in peripheral autonomic indices. HEP recording provides a feasible approach for studying brain–body dynamics during acute sepsis.

DECLARATIONS

Code and materials availability

Code for this article is available at https://github.com/neuroUDP/HEP_delirium

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Funding sources had no involvement in any stage of the study, including design, data collection, analysis, interpretation, or manuscript preparation.

Ethics Approval Statement

The study was approved by the Scientific and Research Ethics Committee of the Clinical Hospital of the University of Chile (Approval No. 71) on January 16, 2023, and was conducted in accordance with national regulations and the Declaration of Helsinki.

Consent to Participate

All participants, or their legally authorized representatives when patients were unable to provide informed consent due to their clinical condition, signed a written informed consent form prior to participation.

Consent for Publication

All authors consent to the publication of this article. The authors declare that no permissions were required to reproduce material from external sources.

Authors' Contributions

EA and FJP designed the study. EA acquired and organized all data. EA and FJP conducted the data analysis. EA prepared all tables, and FJP generated the visualizations. EA wrote the first draft of the manuscript. EA and FJP revised and prepared the final version for submission. GC and AP supervised the study design, contributed to the manuscript development, and reviewed the final text. All authors approved the final manuscript.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT (powered by OpenAI's language model, GPT-5; http://openai.com) in order to improve the grammatical accuracy of the submitted manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication. Selected paragraphs were submitted to ChatGPT with the prompt "Consider the following text ["TEXT"]. Shorten it without losing information, do any modifications necessary to improve grammatical clarity and readability". The results were copied into the manuscript body and edited/adjusted to fit the authors' writing style. Sometimes, ChatGPT would make changes that did not express the authors' ideas, and these were discarded.

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ARTICULO 3

Bodily and Cognitive Experience in Patients With Sepsis and Delirium or Subsyndromal Delirium

Nursing in Critical Care

WILEY | BACCN

RESEARCH ARTICLE

Bodily and Cognitive Experience in Patients With Sepsis and Delirium or Subsyndromal Delirium

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Keywords: body image | cognition | delirium | grounded theory | sepsis-associated encephalopathy

ABSTRACT

Background: Sepsis often causes cognitive changes like delirium and subsyndromal delirium (SSD). Delirium involves acute cognitive dysfunction, while SSD presents partial symptoms. Both conditions impact prognosis and are linked to neuroinflammation, altered cerebral perfusion and neurotransmitter dysfunction. This study explores the embodied cognitive experience in sepsis, integrating enactivist perspectives on the dynamic interplay of body, environment and neural activity.

Aim: To analyse the lived bodily and cognitive experiences of patients with sepsis who experienced delirium or SSD.

Study Design: A qualitative grounded theory study was conducted in a university hospital in Santiago of Chile. Adults with sepsis meeting SEPSIS-3 criteria and meeting at least one criterion on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) positivity were included. Data were analysed using Corbin and Strauss's approach, applying open and axial coding to identify cognitive and bodily experience patterns.

Findings: Ten semi-structured interviews (nine patients) were conducted before discharge. The study identified 20 subcategories of patients' bodily and cognitive experiences with delirium or SSD. In terms of bodily experiences, patients reported somatic depersonalization and loss of bodily control; pain and discomfort led to postural adjustments and eye closure as coping mechanisms. In the case of cognitive experiences, participants experienced visual hallucinations, distorted reality, disorientation and difficulty verbalising thoughts or understanding healthcare providers. Patients opened their eyes to confront visual stimuli and gradually recognized hallucinations as unreal, helping them reconnect with reality. Reported consequences following delirium or SSD included fragmented memories, fear of recurrence and perceived cognitive and physical decline.

Conclusions: Patients with sepsis and delirium or SSD experience disruptions in the lived body, including bodily and cognitive aspects such as pain, depersonalization, hallucinations, disorientation and communication difficulties, affecting emotional and cognitive functioning.

Relevance to Clinical Practice: This study points to the need for non-pharmacological interventions that address cognitive, bodily and environmental aspects. Patient-centred care should ensure accessible environments and adequately trained personnel to support individuals experiencing delirium and SSD.

Impact Statements

- What is known about the topic
  - Sepsis causes delirium and subsyndromal delirium (SSD), both involving acute cognitive dysfunction, including attention deficits, disorientation or altered states of consciousness.
  - Physiological mechanisms—such neuroinflammation, cerebral perfusion changes and neurotransmitter imbalances—contribute to the onset and severity of delirium and SSD, worsening patient outcomes.
  - Environmental (e.g., noise, lighting, overstimulation) and physical stressors (e.g., immobility, pain) are known precipitants of delirium.
- What this paper adds
  - This study provides qualitative insights into the lived experiences patients with sepsis and delirium or SSD, revealing disruptions in the lived body, including pain, somatic depersonalization, hallucinations, disorientation and communication difficulties—affecting emotional and cognitive functioning.
  - It emphasises the value of an enactivist perspective by linking bodily disturbances to cognitive disruptions, highlighting how SSD can resemble delirium in subjective experience.
  - The study identifies patient-reported coping strategies (e.g., eye-opening, environmental orientation) and highlights the relevance of implementing non-pharmacological interventions for patients with delirium or SSD. Person-centred communication and care are emphasised as key approaches to address both bodily and cognitive symptoms.

1 | Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a deregulated host response to infection [1]. This condition is associated with cognitive changes, with delirium being one of the most frequent complications [2–4]. Delirium is an acute cognitive impairment characterised by disturbances in attention, consciousness, and various cognitive functions, such as memory, disorganised thinking, spatiotemporal disorientation and altered perception [5]. The pathophysiology of sepsis-induced delirium involves neuroinflammation, cerebral perfusion alterations, blood–brain barrier dysfunction and neurotransmission disorders [2].

Additionally, many patients present partial manifestations of delirium [6], such as inattention, disorientation, changes in awareness level, without fulfilling all diagnostic criteria [6]. These patients are diagnosed with subsyndromal delirium (SSD) [7], recognised as part of a continuum of acute brain dysfunction, with delirium syndrome representing the more severe end of the spectrum [8, 9]. In patients with sepsis, SSD has been reported in association with neuroinflammatory mechanisms triggered by infections. For example, patients with urinary tract infections showed a significantly higher risk of SSD [10]. Furthermore, specific objective indicators, such as elevated C-reactive protein (CRP) levels and a body temperature $\geq 37.5°C$, have been associated with infection and the onset of SSD [11, 12].

Considering the physiological and behavioural changes associated with delirium and SSD, this study examines how these alterations influence the subjective bodily and cognitive experiences of patients with sepsis.

2 | Background

The conditions observed in patients with sepsis and delirium or SSD highlight the interplay between subjective experiences, physiological changes and cognitive processes, emphasising the need for theoretical approaches that integrate these dimensions. In this context, contemporary enactivist frameworks [13–15] offer valuable perspectives for understanding this interaction, as they propose that cognition cannot be understood in isolation at the cerebral level but instead emerges from the dynamic interaction between the body, the environment, and neural activity [16]. According to this model, cognition is intrinsically linked to bodily experience, suggesting that various cognitive and perceptual alterations should have a corresponding bodily correlation [14]. These approaches posit that the body is the locus of the subject—that is, the patients with sepsis—the source, and the medium of their relationship with the world, integrating biological processes with subjective experience [15].

Following this perspective, Merleau-Ponty and later scholars such as Thomas Fuchs conceptualised the interrelation between the 'living body' and the 'lived body'. The 'living body' refers to the biological and physiological processes—the body's objective, and measurable functions. In contrast, the 'lived body' pertains to subjective experience, which acts as a background and becomes evident when attention is directed toward bodily sensations, particularly in states of disturbance such as fatigue or illness. In such cases, the body ceases to be a transparent medium for engaging with the world and becomes the focal point of experience [15]. This distinction helps to understand how physiological changes in the 'living body' can alter the knowledge of the 'lived body' and its relation to cognitive processes.

In patients with sepsis and delirium or SSD, objective alterations such as changes in body temperature, heart rate, respiratory rate and white blood cell count (>12000 per ml or <4000 per mL) have been observed [17]. These physiological changes may influence subjective bodily experience and cognitive processes.

3 | Aims and Research Questions

This study addresses the following question: How do patients with sepsis who have experienced delirium or SSD perceive and experience their lived body, considering both bodily and cognitive dimensions?

The primary aim of this study is to analyse the experience of the lived body, considering both bodily and cognitive dimensions, in patients with sepsis who presented with delirium or SSD.

The secondary aims are as follows:

i. To describe bodily perceptions during episodes of delirium or SSD, identifying sensations, limitations and changes in perception.

ii. To describe the cognitive experiences associated with delirium or SSD, including attention, memory, thinking and consciousness alterations.

4 | Design and Methods

A qualitative study was conducted using the systematic grounded theory approach of Corbin and Strauss [18] to explore the bodily and cognitive experience of patients with delirium or SSD, following the Guidelines for Reporting and Evaluating Grounded Theory Research (GUREGT) [19]. The structured analytical procedures proposed by Corbin and Strauss were complemented by a reflexive, constructivist orientation to ensure both methodological rigour [20]. Grounded theory enables the description of human behaviour-related phenomena to generate theories, concepts and hypotheses based on data and case studies using an inductive process. Focusing on theory development, this design involves simultaneous data collection and analysis [21].

4.1 | Setting and Sample

This study was conducted in a university hospital in Santiago, Chile, involving patients admitted to the intermediate and surgical-medical intermediate care units. Participants met the SEPSIS-3 diagnostic criteria, confirmed by a Sequential Organ Failure Assessment (SOFA) score > 2 points [1].

The sample included patients over 18 years old, admitted with renal, abdominal or respiratory sepsis, who met at least one of the four positive criteria of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)—acute or fluctuating change, inattention, disorganised thinking or altered consciousness—within the first 3 days of hospitalisation. Patients with acute or fluctuating change and inattention, plus either disorganised thinking or altered level of consciousness, were classified as having delirium. Those with only one or two isolated CAM-ICU alterations, without meeting full criteria, were classified as having SSD [7].

All patients were invited to participate upon admission, before the onset of delirium symptoms and were followed up on Days 2 and 3 to assess whether they developed delirium or SSD.

Exclusion criteria included patients with COVID-19, chronic liver disease, cardiovascular instability (norepinephrine > 0.3 μg/kg/min), urgent intubation, pre-existing cognitive impairment (AD8 > 2) or those in palliative care or end-of-life care. Patient characteristics are presented in Table 1.

4.2 | Data Collection Tools and Methods

The primary researcher conducted individual interviews to collect data from July to December 2024. CAM-ICU was administered to ensure that the patient was fit to participate in the

TABLE 1 | Characterisation of patients admitted to the study.

ID	Age	Sex	Years of schooling	Reason for admission	CAM-ICU to recruitment	Person who accepted informed consent	Days hospitalised	Days symptoms of delirium	Symptoms of delirium on Day 2
1	54	F	16	Abdominal sepsis	−	Patient	13	2	a, b, c, d
3	43	M	15	Abdominal sepsis	−	Patient	6	2	a, b
4	74	M	12	Abdominal sepsis	+	Son	6	3	a, b
5	55	F	20	Renal sepsis	−	Patient	15	3	a, b
6	89	F	7	Abdominal sepsis	+	Daughter	20	4	a, b
9	73	F	8	Respiratory Sepsis	−	Patient	22	1	a, b, c
11	60	M	9	Respiratory Sepsis	−	Patient	6	7	a, b
12	70	F	9	Abdominal sepsis	−	Patient	9	1	a, d
19	70	F	8	Abdominal sepsis	+	Daughter	17	2	a, b, d

Note: a, acute onset or fluctuating course; b, inattention; c, disorganised thinking; d, altered level of consciousness; F, feminine; M, masculine.

interview. Interviews were conducted with patients who were negative on the CAM-ICU.

Each interview lasted between 40 and 127 min. Fieldwork and data analysis were supervised by a qualitative research expert (P.O.). The interviews were conducted the day before hospital discharge, within the hospital setting, in a room with appropriate lighting, noise control, temperature regulation and privacy.

A semi-structured interview format was used, consisting of an introduction, core questions and a conclusion. Participants were encouraged to share their experiences freely. The interview questions (Table S1) were developed based on a theoretical review of the lived body, clinical expertise and prior research and were reviewed by qualitative research experts. Interviews maintained a respectful approach, and education about delirium and SSD was provided at the end by the primary researcher. This considers general theoretical aspects and home management strategies, as well as other emerging issues identified during the interview. All interviews were audio-recorded, transcribed and written notes were taken.

The audio recordings were transcribed verbatim. Four researchers, working in pairs (E.A., N.C. and R.O., V.V.) independently transcribed and reviewed the same interview. Each researcher numbered the lines and compared the text. Data files were stored in password-protected folders, with each interview assigned a unique identification code.

4.3 | Data Analysis

Transcribed data were analysed following Corbin and Strauss's grounded theory method [19].

Open coding was performed by independently labeling words, sentences and events related to predefined categories—(a) body experience during hospital processes (subcategories body perception, body control, interaction with environment) and (b) interaction with environment and cognition (content and structure of thought, cognitive components, changes in the state of consciousness)—as well as emergent, nonspecific category. Each category and subcategory is detailed in Table S2.

This process was conducted in pairs (E.A., N.C. and R.O., V.V.), where each researcher performed line-by-line coding independently, followed by a comparison to verify category assignments. The research team then conducted group discussions to review and solve coding differences.

All identified excerpts were compiled, and each patient's registration code and interview line number were recorded for each category and subcategory (Table S3). This process generated a summary table, leading to the open coding count table (Table S3).

The coding paradigm of Strauss and Corbin was used for axial coding [19], with the following elements:

i. Phenomenon,
ii. Causal conditions,
iii. Context,
iv. Action strategies and
v. Consequences.

Categories, subcategories and excerpts were organised according to these elements. The researchers connected categories and identified patterns in the relationship between bodily and cognitive experiences during the first days of hospitalisation, aiming to analyse the key aspects of the phenomenon under study.

Memos and diagrams were used to visualise relationships among data, codes, categories, participants and interviewers. The results included tables, figures, narratives and quotations.

4.4 | Rigour

Methodological rigour was ensured by integrating the systematic and constructivist approaches of grounded theory.

From a systematic grounded theory perspective, rigour was addressed both before and during analysis. Researchers engaged in theoretical preparation and reflexive awareness to remain receptive to participants' meanings. During the analysis, the principles of constant comparison, theoretical sensitivity and conceptual density guided the development and refinement of categories, ensuring they remained data-grounded and conceptually coherent.

From a constructivist grounded theory perspective, rigour was ensured through the criteria of credibility, originality, resonance and usefulness. Credibility was supported through triangulation of data sources, peer review of transcripts and analyses and verification of verbatim quotations against audio recordings to preserve participants' voices. Originality emerged from addressing conceptual gaps in the literature on sepsis, delirium and embodied cognition. Resonance was enhanced by integrating detailed textual accounts of patient narratives, ensuring that the findings reflected experiences recognizable to both participants and clinicians. Usefulness was demonstrated through the clinical implications of understanding embodied and cognitive experiences in sepsis and delirium or subsyndromal delirium, providing a theoretical basis for future research and intervention design. This integrative approach combined analytical rigour with reflective depth, harmonizing systematic analysis with participant-centred interpretation.

4.5 | Ethical Considerations

The study was approved by the Scientific and Research Ethics Committee of the Hospital Clínico de la Universidad de Chile in Santiago, Chile (approval no. 071/2023) on 19 October 2023. Participants were invited during the first hours of hospitalisation, where the study was explained and general information about the research process was provided.

Given the characteristics of the clinical condition under study, a recall bias may have been introduced during the process. However, several actions were taken to ensure participant involvement and the protection of their rights, in accordance with

the hospital's ethics committee guidelines. These measures are detailed below.

- Consent was obtained verbally and in writing, ensuring voluntary participation and the right to withdraw. A copy of the consent form, including contact information, was provided to participants. Confidentiality was maintained through restricted digital storage of study data.
- CAM-ICU was administered at three time points. Initially, it was used to evaluate cognitive capacity prior to obtaining informed consent. In the event of a negative result, the patient provided consent; if positive, consent was obtained from a legally authorised representative. The second assessment occurs during hospitalisation to check the presence of delirium or SSD. The final evaluation was conducted before the interview to confirm that the patient possessed an adequate level of consciousness. Only those patients demonstrating a negative result at this stage were considered eligible for interview participation.

Education about delirium and SSD was included at the end of the interview, with patients being informed about general theoretical aspects of their own experience and options for managing it at home, including other emerging issues related to this research identified during the interview.

5 | Findings

The results are presented considering the open and axial coding of the grounded theory framework. Through open coding, 9 categories and 20 subcategories were identified and subsequently reorganised. These are presented in the Counting Table (Table S3). According to the coding paradigm [19], the axial coding process considers the following elements: phenomenon (7 subcategories), causal conditions (2), contextual conditions (1), strategies (2) and consequences (3). These components are described below, accompanied by a representative quote for each subcategory (Figure 1). An explanatory model of bodily and cognitive experiences in delirium and SSD is presented under an axial coding structure. Additional quotes are in the Table S4.

5.1 | Phenomenon

The phenomenon corresponds to identifying what is happening, in this case, the symptoms of delirium or SSD experienced by patients at the bodily and cognitive levels during the first days of hospitalisation.

5.1.1 | Bodily Level

5.1.1.1 | Somatic Depersonalization. Patients experienced a shift in their perception of their bodies, manifested in several ways, such as feeling their bodies as strange, foreign or unrecognisable.

> I actually felt my body, because sometimes it felt like floating and sometimes like drowning, as if being underwater in a pool.
>
> (E8, 221–223)

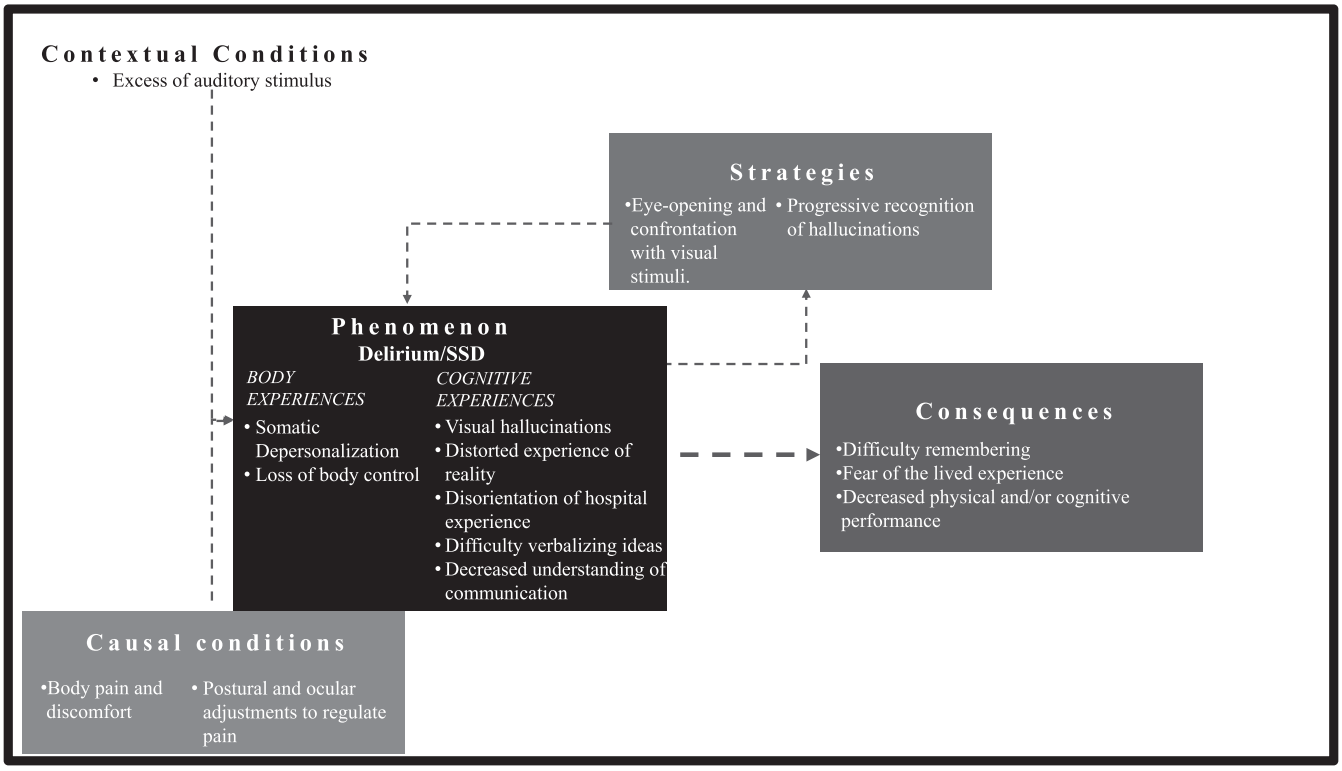

FIGURE 1 | An explanatory model of bodily and cognitive experiences in patients with sepsis and delirium or subsyndromal delirium. Axial Coding.

5.1.1.2 | Loss of Bodily Control. During those days, patients experienced decreased bodily function, including the perception of mastery and control over their bodily capabilities. Restricted mobility due to pain was particularly notable, leading them to adopt passive postures.

> Blockage was like... trying not to speak too much and just being still, expressing how my pain felt for me.
>
> (E3, 68–69)

5.1.2 | Cognitive-Perceptual Level

5.1.2.1 | Visual Hallucinations. The reported visual hallucinations contained abstract images, people or situations disconnected from reality.

> When everything was over, first I saw many yarn balls, beautiful pastel-colored balls that were forming into a large circle...
>
> (E1, 36–39)

5.1.2.2 | Confused and Distorted Experience of Reality. Patients described a series of confusing sensations and experiences of estrangement related to the bodily and social environment. These experiences included (i) feeling like they were in other places; (ii) confusion between dreams and reality; or (iii) feeling like they were in a movie.

i. Being in other places. Some patients experienced the sensation of being in different spaces, such as a house or an imagined environment, failing to recognise the hospital setting.

> I felt like I was in a house and kept wondering why that was there and why I was in this house's living room; and then I realized that it was just my imagination.
>
> (E8, 124–127)

ii. Dream-reality confusion. Dream experiences blended with reality, making it difficult for patients to distinguish between what they had dreamed and what had actually happened, creating a sense of uncertainty.

> One day I really can't tell if I was just dreaming. There were these guys... [nurse aides] one was standing here and I don't know whether he was actually there or if I just felt like he was.
>
> (E6, 82–84)

iii. Feeling like in a movie. Some patients described their hospital experience as being in a movie, where events seemed unreal, and their perceptions failed to integrate coherently.

> It was like a movie. I was unable to retain what I saw, and a myriad of things were just spinning around all the time.
>
> (E2, 298–299)

5.1.2.3 | Disorientation in the Hospital Experience. Patients reported experiencing spatial, personal and temporal disorientation, struggling to understand their environment or process their situation, leading to confusion regarding their hospital stay. A recurrent theme was the feeling of being lost.

> I couldn't figure out where I was, I couldn't find my bearings.
>
> (E6, 23)

5.1.2.4 | Mental Block and Difficulty Verbalising Thoughts. Patients reported a loss of control over their cognitive abilities, describing a state of 'mental block' that impaired their ability to organise and/or express thoughts. They described having thoughts but being unable to verbalise them.

> What was going on around me? Why was I like that? The question had no answers, because apparently my words didn't go through. I was only thinking that I was going to talk, but then I didn't.
>
> (E8, 233–235)

5.1.2.5 | Reduced Comprehension of Healthcare Communication. Patients described feeling disconnected during conversations with healthcare staff and finding explanations confusing, distant, or difficult to process, which hindered their understanding of their situation. They also reported difficulty retaining information, especially in lengthy or complex messages.

> When they talked to me, I could hear, but it came like from far away.
>
> (E3, 31)

5.2 | Causal Conditions

These factors represent potential triggers for the onset or progression of the phenomenon. Here, we outline patients' clinical events and adaptive challenges before developing delirium symptoms, focusing on physical manifestations.

It is important to emphasize that these causal factors are derived directly from our study's patient narratives, reflecting their experiences and perceptions of contributing events.

5.2.1 | Pain and Discomfort Associated With Medical Conditions and Clinical Symptoms

Before and during the first hours of hospitalization, patients reported pain and other clinical symptoms related to their medical diagnoses, such as nausea and vomiting, leading to generalized discomfort.

> My back hurt, I touched my belly, and it hurt; vomit; I was nauseated. That's how I was when I got here.
>
> (E6, 9)

5.2.2 | Pain Control Through Postural and Ocular Adjustments

Patients adopted comfortable or analgesic postures to minimize pain-related bodily discomfort.

> ...trying to put my body ... in a position where my stomach didn't hurt ...
>
> (E7, 74–75)

Additionally, another emerging strategy to mitigate pain or disconnect from bodily discomfort and the environment was closing their eyes.

> And it was the only thing I felt. I closed my eyes and focused so that the pain would go away and daybreak would come sooner.
>
> (E7, 93–95)

These strategies may be related to the category of visual hallucinations, corresponding to the phenomenon:

> When I closed my eyes, I could actually feel. I did it to rest my mind; that's how I thought the pain go away, but the pain continued, and I kept seeing those images.
>
> (E1, 116–117)

5.3 | Contextual Conditions

The contextual conditions are the specific circumstances influencing the phenomenon and the strategies. In the case of patient experiences, these conditions relate to the hospital environment.

5.3.1 | Excessive Environmental Stimuli

The constant noise from machines, medical staff, and other patients represented a significant source of discomfort. Invasive sounds, especially conversations or shouting, increased irritability and made rest difficult.

> Noise, noise, so much noise. On top of that, the girl [healthcare worker] talked non-stop.
>
> (E3, 159)

Additionally, some patients described how combined visual and auditory stimuli heightened discomfort and a sense of invasion.

> ...listening to moans, seeing other patients, all of that puts you in a bad mood, right? I tried to close my eyes and shut myself off.
>
> (E7, 146–147)

5.4 | Coping Strategies

Strategies refer to the actions individuals take to resolve or respond to the phenomenon. Among the strategies implemented by patients, the most prominent are opening their eyes (bodily experience) and confronting hallucinations against the lived context (cognitive experience).

5.4.1 | Eye-Opening and Confrontation With Visual Stimuli

Visual stimuli in the hospital environment, such as furniture or lights, serve as anchors that patients use to differentiate between hallucinations and reality. Opening their eyes reinforces their temporal and spatial orientation.

> I was able to figure out that there was something wrong with me. Suddenly, I sort of reacted, thinking 'no, this isn't real'; then I opened my eyes and came back to my reality. Opening my eyes made it seem like just nonsense.
>
> (E1, 44–46)

5.4.2 | Progressive Recognition of Hallucinations

As the days pass, patients gradually recognise that their hallucinations are manifestations of an altered state of consciousness, progressively identifying the reality of the hospital environment.

> Yes, I was able to figure it out, that I wasn't where I thought I was, that I was in the hospital.
>
> (E8, 69–70)

5.5 | Consequences

Consequences refer to both expected and unexpected outcomes of strategic actions, considering the results of an interaction in response to the phenomenon. This study identified the effects patients perceive in the short term after experiencing delirium.

5.5.1 | Difficulty Remembering the Experience

Patients reported experiencing confusion, memory loss or fragmented recollections of their hospitalisation. They mentioned difficulties remembering specific details of their experience, which were often confronted with evidence provided by their relatives.

> My memory... apparently the first day I felt ok, but the other days I was lost and I don't really remember that much.
>
> (E177-178)

5.5.2 | Fear of the Experience

The disorientation, hallucinations and perceived loss of control led patients to feel fear, discomfort and distress in later stages, particularly when recalling these experiences.

> I couldn't believe what had happened to me [hallucinations]... it was like a nightmare.
>
> (E6, 16)

> You could say that now I feel uncomfortable; I mean, you don't know what is going on [during the delirium episode]. Never before had I gone through something like that, seeing things or having my head spinning around.
>
> (E2, 144–147)

5.5.3 | Decreased Physical and/or Cognitive Performance

Patients with delirium described a sensation of decline and slowing down of their physical and cognitive abilities after hospitalisation. Physically, they reported a loss of strength and a general perception of weakness, even when considered clinically recovered. Cognitively, they described difficulties with memory, comprehension and other functions.

> No, sometimes I'm perfectly oriented, and I suddenly go out, and I don't know where I am anymore.
>
> (E3, 129)

6 | Discussion

This study explored the bodily and cognitive experience of patients with sepsis and delirium or SSD from an enactivist perspective. Considering delirium and SSD as a continuum of acute brain dysfunction, the findings reveal alterations in bodily and cognitive perception and consequences perceived. Clinical implications and limitations are discussed.

6.1 | Bodily Experience at Hospital Admission and During Delirium or SSD

Patients described postural and ocular adjustments as strategies to relieve pain and discomfort upon hospital admission, which were identified as causal conditions preceding the onset of delirium or SSD. These strategies reflect the dynamic interaction between the body and cognition, supporting that cognition emerges from the interaction between the body, the environment and neural activity [16].

During delirium or SSD, patients experienced somatic depersonalization and loss of bodily control, reflecting how the lived body becomes the focus of experience in response to bodily or cognitive disturbances [15]. Previous studies conducted in laboratory settings have shown that pain [22, 23] and immobility [24] alter body perception. Research on body representation modifications indicates that the perception of transparent limbs reduces the sense of ownership and pain [22, 23]. These findings highlight the importance of considering bodily experience in managing delirium and SSD.

6.2 | Cognitive and Perceptual Experience in Delirium or SSD

Upon hospital admission, patients did not report cognitive changes, but during the first few days, they experienced alterations such as visual hallucinations, distorted reality and spatial and temporal disorientation. These findings align with the literature defining delirium as an acute cognitive dysfunction [5].

This study provides a subjective perspective on how patients with sepsis experience these alterations, also present in SSD. Additionally, the patients reported difficulties in verbalization, fluency, and language comprehension, possibly related to executive functions [25]. These changes affect interaction with the environment, highlighting the need to adapt communication and provide additional support for patients with delirium and SSD [26].

6.3 | Strategies and Consequences for Subjective Experience

Patients used strategies such as opening their eyes and gradually recognising hallucinations to regain control and distinguish between reality and illusions. Interaction with the physical environment, mainly through visual stimuli, facilitated reorientation and reduced confusion. This process could be key to developing non-pharmacological strategies for delirium prevention [27]. These findings are consistent with previous studies emphasizing the importance of coping strategies and the impact of the hospital environment on delirium management [28, 29].

In the short term, patients in this study reported difficulties remembering events, fear of reliving the experience, distress and perceived cognitive and physical decline. Similar findings have been reported in studies from Sweden [30], Iran [31] and Italy [32], as well as in reviews describing post-intensive care distress [33] and memory problems [34]. These findings reinforce the association with post-intensive care syndrome (PICS) and underscore the need for early strategies and follow-up interventions to mitigate its effects [35].

7 | Limitations

This study provides an in-depth understanding of the bodily and cognitive experience of patients with sepsis and delirium or SSD, but has several limitations. The qualitative design and sample size allow for a detailed exploration of this experience; however, it is recommended to complement this with quantitative research to obtain more generalizable results. For a more comprehensive perspective, it could be worthwhile to use mixed-methods research that can integrate subjective experience with objective data, such as cognitive assessments, brain monitoring, heart rate or inflammatory markers.

The study was based on interviews conducted after hospital discharge, which may introduce recall bias. Although full control of variables was not feasible, several measures were implemented to minimise potential bias; these actions are detailed in the section on ethical considerations. Future studies should rely on real-time methods such as diaries, audiovisual recordings or mobile applications to capture patients' experiences during delirium and analyse the temporal evolution of symptoms.

Additionally, the study did not differentiate motor function based on the type of delirium and SSD, which could influence bodily and cognitive perceptions. However, patient experiences in this study are similar to those reported by other studies on hypoactive delirium [30]. These patients described feeling trapped in a distorted reality, unable to distinguish between real and illusory experiences, with vivid hallucinations. Furthermore, they reported confusion, memory loss, nightmares, and a profound sense of disconnection, exacerbated by communication difficulties and a feeling of isolation from healthcare staff and family [30].

This study underscores the need to approach delirium and SSD comprehensively, considering both bodily and cognitive aspects. Future research should continue exploring this interrelation through mixed-method approaches and long-term follow-ups to develop more effective patient-centred interventions.

8 | Recommendations and Implications for Practice

Delirium and SSD have distinct diagnostic criteria, but their transition is diffuse, as SSD patients exhibit bodily and cognitive changes and consequences similar to those in delirium. SSD may represent an early or less severe stage of delirium, as patients exhibit similar bodily and cognitive alterations. Early delirium prevention focuses on early mobilisation, environmental management and cognitive stimulation [36–39]. Given these overlaps, interventions for delirium may also benefit patients with SSD. This study underscores the importance of addressing patients' subjective experiences—such as communication difficulties and loss of bodily control—to enhance the relevance of

TABLE 2 | Proposed interventions for bodily and cognitive changes in patients with sepsis and delirium or subsyndromal delirium.

Components of grounded theory	Categories identified in patients with delirium and SSD	Intervention considerations	Examples for intervention
Casual conditions	Body pain Pain regulation with postural and ocular adjustments.	Pain protocol [36–38]	– Standardised pain protocol, preventive analgesia, pharmacological and non-pharmacological strategies
Contextual conditions	Excess of auditory stimulus	Environmental management [37, 39]	– Monitor noise levels in patient rooms, reduce auditory stimuli at night, adjust lighting based on time of day, provide visual aids like clocks and calendars, ensure cognitive accessibility with clear, predictable and understandable information and environments
Phenomenon	*Cognitive experiences* Visual hallucinations, distorted experience of reality, disorientation of hospital experience, difficulty verbalising ideas, decreased understanding of communication *Body experiences* Somatic Depersonalization, loss of body control	Patient-centred communication [26] Monitoring delirium [36–38] Early mobilisation [38] Cognitive stimulation [27, 36, 37, 40]	– Empathetic, clear explanations, validation of patient experience, considering individual needs and emotions. – Daily assessment of delirium – Body awareness activities, passive and active range of motion exercises, bed mobility and sitting up in bed, transfers to chairs and sitting out of bed, assisted standing and walking, task-oriented physical activities – Training of cognitive functions (orientation, attention, memory, executive functions, praxis)
Strategies	Eye-opening and confrontation with visual stimuli Progressive recognition of hallucinations	Patient-centred communication [26] Environmental management [37, 39]	– Promote environmental awareness, active listening to the patient's experience, empathy and clear and simple explanations of procedures – Maintain a calm environment with clear, understandable and predictable visual cues
Consequences	Difficulty remembering Fear of the lived experience Decreased physical and/or cognitive performance	Post intensive care syndrome (PICS) assessment and monitoring [35]	– Screening before discharge – Psychoeducation for patient/family during hospitalisation and follow-up to discharge.

intervention and support both neurocognitive recovery and embodied, emotional aspects of care.

Second, patient-centred communication is a relevant approach for individuals experiencing delirium and SSD. It involves tailoring communication to the patient's needs, values and emotions [40]. This includes using short, simple and clear language; showing empathy through active listening; providing orientation about personal, temporal and spatial situations; acknowledging hallucinations or confusion; offering emotional support by maintaining a calm and gentle tone; and involving the patient and family in care decisions [26].

Finally, it emphasises considering patients' subjective experiences in designing interventions. The interviews and quotes revealed how delirium and SSD impact patient experiences and highlighted the need for healthcare teams to address these effects. Understanding how patients experience delirium and SSD will facilitate the development of more effective prevention and management strategies. Table 2 suggests a specific plan based on grounded theory to address these aspects.

9 | Conclusion

This study shows that patients with sepsis and delirium or SSD experience disruptions in their lived body, including pain, depersonalization, loss of control and cognitive symptoms such as hallucinations, disorientation and communication difficulties. These interrelated experiences impact emotional and cognitive functioning. The findings support integrated care approaches that address both physical and cognitive dimensions of the patient experience, emphasising the person-centred, non-pharmacological interventions.

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Ethics Statement

This study was approved by the Scientific and Research Ethics Committee of the Hospital Clínico de la Universidad de Chile (approval no. 071/2023), 19 October 2023.

Consent

Informed consent was obtained from all study participants or their legal representatives. The study complies with the ethical principles outlined in the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Analisis at https://drive.google.com/drive/folders/1Z6N4Uid1LCSJwMMCNv1XlskgJl4FGUDh?usp=sharing. Additional data may be available from the corresponding author upon reasonable request; some data may be subject to ethical or confidentiality restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Interview script. **Table S2:** A priori categories, subcategories, colour codes and analytical details. **Table S3:** Open coding frequency. **Table S4:** Open coding frequency.

V. DISCUSIONES Y CONCLUSIONES

Contextualización del problema y relevancia del estudio

El delirium asociado a sepsis constituye una de las complicaciones neurocognitivas más prevalentes, complejas y con mayor impacto funcional en pacientes críticos. Su fisiopatología implica una combinación de neuroinflamación, disfunción autonómica y alteraciones de la actividad cortical, lo que sugiere una disrupción profunda en los mecanismos que integran cuerpo, cerebro y experiencia consciente. No obstante, la literatura tradicional aborda estos niveles por separado: estudios fisiológicos que examinan señales autonómicas aisladas, investigaciones neurofisiológicas centradas en el EEG, y trabajos cualitativos que describen la confusión o desorientación subjetiva sin vincularla con mecanismos corporales.

En este escenario, comprender el delirium desde la perspectiva de la cognición corporeizada resulta relevante. Este marco propone que la conciencia se sostiene en una circularidad continua entre el cuerpo vivo (procesos fisiológicos, autonómicos y viscero–cerebrales) y el cuerpo vivido (experiencia subjetiva, percepción corporeizada, interacción entre procesos neuro-fisiológicos y mentales). Esta tesis se inscribe en ese paradigma y estudia el delirium asociado a sepsis a través de tres niveles complementarios:

1. alteraciones autonómicas,
2. integración corazón–cerebro mediante HEP,
3. vivencias corporales y cognitivas de los pacientes.

Discusión y reflexiones de cada artículo

A continuación, se analizarán los artículos considerando sus principales hallazgos, la relevancia y discusión de estos resultados, su integración en relación con la pregunta de investigación de la tesis doctoral y las limitaciones identificadas en cada estudio.

Artículo 1

Síntesis de hallazgos

El análisis de los estudios incluidos muestra que el delirium se acompaña de alteraciones frecuentes en distintos dominios del sistema nervioso autónomo. A nivel cardiovascular, los hallazgos fueron heterogéneos en HRV, consistentes en el aumento de la variabilidad de la presión arterial (BPV) y en la reducción de la presión arterial media (MAP), indicando inestabilidad hemodinámica durante el episodio. En el dominio ocular, todos los estudios reportaron disminución de las velocidades de constricción y dilatación pupilar.

En el ámbito gastrointestinal, se observó disminución de la diversidad microbiana y un perfil más inflamatorio, mientras que en el dominio neuroendocrino se identificaron niveles periféricos elevados de norepinefrina. En conjunto, estas alteraciones describen un patrón de variabilidad autonómica multisistémica que coexiste con el delirium, aunque sin definir un perfil fisiológico único debido a la heterogeneidad de métodos, poblaciones y contextos clínicos.

Discusión del artículo

Los hallazgos de este scoping review amplían la comprensión tradicional del delirium, habitualmente centrada en identificar alteraciones neurocognitivas o

dinámicas neurofisiológicas en redes del sistema nervioso central (Inouye et al., 2014; J. E. Wilson et al., 2020). En contraste, esta revisión buscó identificar patrones fisiológicos recurrentes reportados durante el episodio. Los resultados muestran que el delirium se acompaña de inestabilidad autonómica en múltiples dominios corporales, configurando un patrón distribuido de variabilidad fisiológica que sugiere cambios regulatorios más amplios, sin delinear un mecanismo único o uniforme.

La heterogeneidad observada en HRV refleja la diversidad de poblaciones y métodos, pero los patrones más consistentes —incremento de BPV y disminución de MAP— se alinean con modelos que plantean el delirium como un estado de disminución de la integración hemodinámica, donde la estabilidad de las oscilaciones cardiovasculares se vuelve vulnerable y potencialmente susceptible a fluctuaciones en la perfusión cerebral (Liu et al., 2024; Stulberg et al., 2023) .En el dominio pupilar, las alteraciones observadas son coherentes con la organización neuroanatómica del reflejo pupilar (Peinkhofer et al., 2019), y sugieren un compromiso transitorio en los circuitos troncoencefálicos responsables del arousal y la regulación autonómica. Los cambios gastrointestinales y la reducción de la diversidad microbiana, por su parte, parecen estar vinculados a una activación inflamatoria sistémica más que a una señal directa del sistema nervioso autónomo (Bonaz et al., 2018; Cryan et al., 2019).

Estos resultados permiten comprender el delirium como un estado fisiológico distribuido, en el cual múltiples dominios del cuerpo vivo presentan una regulación fluctuante. Esto complementa la literatura que conceptualiza el delirium como un trastorno multisistémico (Maldonado, 2018; J. E. Wilson et al., 2020), sin embargo,

esta revisión no pretende proponer mecanismos causales, sino mostrar la evidencia disponible a nivel autonómico

Integración del articulo a pregunta de investigación

El Artículo 1 contribuye directamente a la pregunta de investigación de esta tesis al caracterizar las alteraciones autonómicas que emergen en el cuerpo vivo durante el delirium. Desde el marco de Fuchs (2020), el cuerpo vivo constituye la base fisiológica que sostiene la experiencia mediante una circularidad estructural, en la cual los procesos autonómicos posibilitan la percepción, la orientación y la cognición.

Los hallazgos del Artículo 1 muestran que esta base fisiológica del cuerpo vivo puede volverse transitoriamente frágil: la variabilidad hemodinámica, las alteraciones pupilares, los cambios inflamatorios asociados a la microbiota y la elevación de marcadores neuroendocrinos reflejan un desajuste en los mecanismos *hemodinámicos* que mantienen la estabilidad autonómica. Esta fragilidad compromete la circularidad estructural y abre un espacio en el que la experiencia (el cuerpo vivido) puede tornarse inestable, desorganizada o fragmentada.

Si bien el Artículo 1 no examina directamente la circularidad causal, sus resultados permiten situar cómo la experiencia subjetiva (fluctuaciones atencionales, desorientación, alteración del sentido corporal) podría, a su vez, influir sobre los procesos reguladores del cuerpo vivo, generando un proceso recíproco en el que fisiología y experiencia se perturban mutuamente. Este vínculo aparece con mayor claridad en las experiencias descritas por los pacientes en el Artículo 3.

En conjunto, el Artículo 1 establece la base fisiológica para comprender el delirium como un fenómeno encarnado en el que la integración organismo–cerebro–mundo se vuelve frágil. Sus hallazgos permiten conectar las variaciones del cuerpo vivo con

las transformaciones subjetivas del cuerpo vivido, constituyendo el primer nivel del análisis multinivel que organiza esta tesis.

Limitaciones

En términos temáticos, el scoping review incluyó estudios con amplia heterogeneidad metodológica. Los trabajos difieren en los dispositivos utilizados, la duración y frecuencia de los registros, análisis, características de las poblaciones, gravedad clínica, comorbilidades, entre otras. También se observaron variaciones en los instrumentos diagnósticos de delirium y en la temporalidad de las evaluaciones, lo que restringe la comparabilidad entre estudios. Además, la revisión abordó el delirium en general, sin diferenciar entre etiologías específicas (como sepsis, etiologías quirúrgicas o respiratorias), lo que limita la identificación de perfiles autonómicos asociados a contextos clínicos particulares.

En términos teóricos, la evidencia disponible se centró principalmente en parámetros fisiológicos del sistema nervioso autónomo, sin integrar mediciones que permitieran vincular estos cambios con experiencias subjetivas o perceptuales. La falta de datos que relacionen directamente variaciones autonómicas con la vivencia del delirium impide examinar cómo se manifiestan los procesos de circularidad entre cuerpo vivo y cuerpo vivido.

En términos metodológicos, la mayoría de los estudios incluidos no incorporó registros continuos o mediciones simultáneas entre distintos dominios autonómicos, lo que dificulta caracterizar la dinámica temporal de las alteraciones durante el episodio delirante. Las mediciones neuroendocrinas fueron predominantemente periféricas, sin evaluación de mecanismos centrales, y la ausencia de registros multimodales limita la capacidad de establecer patrones consistentes o inferencias causales.

Artículo 2

Síntesis de hallazgos

El estudio evaluó el Heartbeat-Evoked Potential (HEP) en pacientes con SAD y SSD. No se observaron diferencias globales en la amplitud promedio del HEP entre grupos. Sin embargo, el análisis basado en clusters identificó como efecto principal interacciones significativas Grupo × Estado (ojos abiertos vs. ojos cerrados) en dos ventanas temporales: una ventana temprana posterior (120–176 ms), que mostró el efecto más robusto y consistente, y una ventana tardía frontocentral (290–316 ms) significativa, pero con mayor variabilidad. Estos patrones indican una modulación EO – EC alterada en SAD/SSD, especialmente en etapas tempranas del procesamiento cortical de las señales cardíacas.

Los índices de HRV fueron, en general, similares entre grupos, salvo por una reducción del LF/HF en ojos abiertos en el grupo delirium/SSD. Finalmente, los mismos pacientes con SAD/SSD presentaron un menor puntaje total en la Montreal Cognitive Assessment (MoCA) al alta, así como un peor desempeño en los dominios de atención y abstracción.

Discusión del artículo

Los resultados indican que el SAD y el SSD no modifican la amplitud global del HEP, coherente con reportes que muestran estabilidad en la amplitud promedio pese a alteraciones en su modulación estado-dependiente(Coll et al., 2021; Park & Blanke, 2019). Sin embargo, se identificaron diferencias en la modulación EO–EC, particularmente en la ventana temprana posterior (120–176 ms). Este componente temprano del HEP es sensible al foco atencional y al nivel de arousal (Flo et al., 2023; Park & Blanke, 2019), por lo que las diferencias en la magnitud estado

dependiente en delirium/SSD podría relacionarse con modelos que describen inestabilidad cortical y fluctuaciones de conciencia (Maldonado, 2018; van Montfort et al., 2018). La ventana tardía frontocentral (290–316 ms) presentó una interacción significativa, aunque menos consistente, lo que es esperable dado que los componentes tardíos del HEP dependen de funciones cognitivas y atencionales (Flo et al., 2023; Park & Blanke, 2019) que fluctúan considerablemente en el delirium (J. E. Wilson et al., 2020).

Los grupos no difirieron en la mayoría de los índices de HRV, salvo por una menor relación LF/HF en ojos abiertos en delirium/SSD, en línea con la heterogeneidad autonómica descrita en sepsis (Adam et al., 2023; de Castilho et al., 2018). Esto sugiere que las diferencias observadas en el HEP reflejan principalmente ajustes corticales, más que alteraciones autonómicas globales.

Finalmente, el peor rendimiento cognitivo al alta en delirium/SSD (especialmente en atención y abstracción) coincide con evidencia previa sobre secuelas cognitivas tempranas post-delirium (Brummel et al., 2017; Girard et al., 2010; Pandharipande et al., 2013), posiblemente relacionada con la presencia de una reorganización funcional cortical durante la hospitalización.

Integración del articulo a pregunta de investigación

El Artículo 2 aporta evidencia empírica para comprender cómo se modifica la relación cuerpo–cerebro en pacientes con sepsis que desarrollan SAD o SSD. El paradigma de resting state fue adecuado para el contexto clínico agudo, minimizando demandas cognitivas que podrían haber amplificado artefactos (Cisotto & Chicco, 2024).

La alteración en la modulación EO–EC del HEP, especialmente en la ventana temprana, sugiere alteraciones en la forma en que la actividad cortical se ajusta a

cambios sensoriales mínimos, más que cambios en la amplitud global de la respuesta. Esto es congruente con modelos que describen la integración visceral como un componente esencial del mantenimiento de la conciencia y la estabilidad cognitiva (Azzalini et al., 2019; Candia-Rivera & Machado, 2023).

Desde la perspectiva de la cognición corporeizada, estos hallazgos pueden interpretarse como variaciones transitorias en la dinámica de acoplamiento cuerpo–cerebro asociadas al SAD y al SSD en el contexto de la sepsis, reflejadas en cambios en la modulación cortical dependiente del estado. La disminución del rendimiento cognitivo al alta refuerza esta lectura, alineándose con evidencia que describe persistencia de déficits cognitivos post-delirium (Girard et al., 2010; Morandi et al., 2012).

En conjunto, el estudio aporta antecedentes de que el SAD y el SSD se asocian a modificaciones en la modulación cortical dependiente del estado y a alteraciones cognitivas tempranas, situando estos fenómenos dentro de un marco de disrupción de la integración cuerpo–cerebro durante la sepsis.

Limitaciones

En términos temáticos, la muestra del estudio fue pequeña y clínicamente heterogénea, lo que limita la posibilidad de generalizar los hallazgos. La clasificación SAD/SSD se basó únicamente en CAM-ICU, sin distinguir subtipos motores ni considerar trayectorias clínicas específicas que podrían influir en los patrones corticales registrados. Además, el estudio no incluyó un grupo control sin sepsis, lo que impide diferenciar en qué medida las diferencias observadas se asocian al SAS, al SSD o a la condición séptica.

En términos teóricos, el HEP fue interpretado como un indicador de integración cuerpo–cerebro, centrado en la relación entre actividad cardíaca y actividad cortical.

Sin embargo, no se incorporaron mediciones que permitieran vincular estas variaciones corticales con dimensiones perceptuales o experienciales del delirium, en la misma escala temporal del registro, limitando la articulación entre procesos fisiológicos y manifestaciones clínicas.

En términos metodológicos, aunque se diseñó un registro EEG–ECG de seguimiento, no fue posible completarlo en todos los pacientes, especialmente en el grupo control, debido al alta hospitalaria temprana. En consecuencia, el análisis se realizó en un único momento y bajo condiciones controladas de ojos abiertos y ojos cerrados, lo cual no permite capturar la fluctuación temporal propia del delirium. Las mediciones de HRV se obtuvieron en intervalos breves, disminuyendo la estabilidad de algunos índices (Shaffer & Ginsberg, 2017). Finalmente, los efectos detectados mediante análisis basados en clusters requieren replicación en muestras mayores para evaluar su consistencia y robustez (Lakens, 2013).

Artículo 3

Síntesis de hallazgos

Los relatos de los participantes muestran que SAD y SSD se desarrollan como un proceso continuo en el que los cambios corporales iniciales marcan el punto de partida de la alteración experiencia–cuerpo. El dolor, la náusea, el malestar general y los ajustes posturales orientados a disminuir la incomodidad anteceden a modificaciones en la percepción del entorno y en la forma de situarse corporalmente. A medida que el episodio avanza, emergen sensaciones de extrañeza, experiencias de despersonalización somática y pérdida de control motor, junto con alucinaciones visuales, confusión y distorsión de la realidad. Estas

experiencias se acompañan de dificultades para reconocer el espacio clínico, desorientación espacial, temporal y personal, bloqueo en la elaboración y expresión de pensamientos y problemas para comprender la comunicación con el equipo de salud. El contexto hospitalario, con su carga sensorial intensa y fluctuante, contribuye a la dificultad de distinguir entre estímulos internos y externos, intensificando la confusión. Frente a estas alteraciones, los pacientes recurren espontáneamente a acciones para reorientarse, como abrir los ojos, fijar la mirada en objetos reconocibles o buscar señales estables que permitan contrastar lo percibido con el entorno. Una vez superado el episodio, muchos describen recuerdos fragmentados, temor respecto de lo vivido y la sensación de un deterioro físico y cognitivo asociado al proceso. En conjunto, estos hallazgos muestran que los cambios corporales, perceptuales y cognitivos no emergen de manera aislada, sino entrelazados, conformando un proceso dinámico que atraviesa toda la experiencia de SAD o SSD.

Discusión del artículo

Aunque los estudios cualitativos previos sobre delirium han descrito principalmente cambios cognitivos y perceptuales, como confusión, alucinaciones y desorientación (Harding, 2005; Inouye et al., 2014), no han documentado sistemáticamente alteraciones corporales. En este sentido, el Artículo 3 amplía la evidencia disponible al mostrar que pacientes con SAD y SSD (para quienes no existen estudios cualitativos previos) reportan cambios corporales, perceptuales y cognitivos que emergen de manera conjunta durante la sepsis. Las vivencias de extrañeza corporal, despersonalización somática y pérdida de control motor no habían sido descritas previamente en delirium, lo que sitúa la corporalidad como un componente central y poco explorado del episodio delirante.

La teoría de Fuchs ofrece un marco para interpretar estos cambios como una alteración de la circularidad estructural y causal entre cuerpo vivo y cuerpo vivido(2007, 2020). La circularidad estructural muestra cómo la experiencia se funda en la organización fisiológica del cuerpo vivo; así, el dolor, el malestar y las variaciones motoras iniciales pueden condicionar la forma en que se configura la percepción. La circularidad causal describe el proceso inverso: una percepción alterada reorganiza el modo en que el cuerpo se orienta y actúa en el espacio clínico. Esta dinámica se refleja en relatos como “no reconocer el hospital”, “sentirse en otro lugar”, “vivir la hospitalización como en una película” o “no comprender lo que le hablan”. Cuando la integración sensorial y temporal se modifica, la interacción clínica adquiere un carácter fragmentado. En conjunto, los resultados permiten situar la experiencia de delirium y SSD como un proceso intrincado en el que los aspectos corporales, perceptuales y cognitivos se interrumpen y entrelazan, configurando la vivencia durante la sepsis.

Integración del articulo a pregunta de investigación

El Artículo 3 aporta evidencia clave para comprender cómo se expresa la cognición corporeizada en el delirium asociado a sepsis. El estudio mostró que las modificaciones fisiológicas del cuerpo vivo se manifiestan como cambios perceptuales, corporales y comunicativos en el cuerpo vivido, integrando la información del seguimiento clínico con CAM-ICU y de las evaluaciones cognitivas al egreso.

Los relatos indican que variaciones corporales iniciales (dolor, malestar, ajustes posturales) anteceden a transformaciones perceptuales caracterizadas por extrañeza corporal, desorientación, escenas irreales y dificultades para comprender o participar en la interacción clínica. Esto sugiere que la vivencia del delirium

emerge de la interacción entre regulación corporal, integración cognitiva y modos de percibir el entorno.

Desde el marco teórico de Fuchs (2020), este proceso puede entenderse como una alteración simultánea de la circularidad estructural (la fisiología que posibilita la experiencia) y la circularidad causal (la experiencia que reorganiza el cuerpo vivo). Los cambios corporales reorganizan la percepción, y esta percepción reorganizada influye en la orientación, la agencia y el uso del cuerpo en el entorno hospitalario, modificando temporalmente el acoplamiento cuerpo–cerebro–mundo. Así, la experiencia se constituye como un punto de convergencia donde se articulan procesos neuro-viscerales y transformaciones subjetivas.

En conjunto, el Artículo 3 contribuye directamente a la pregunta de investigación al mostrar que SAD y SSD implican un modo alterado de cognición corporeizada, donde lo corporal, lo perceptual y lo experiencial se modifican de manera interdependiente durante la sepsis.

Limitaciones

En términos temáticos, el estudio examinó la experiencia corporal y perceptual de pacientes con sepsis y SAD o SSD mediante entrevistas retrospectivas, lo que introduce la posibilidad de sesgo de recuerdo, ya que las vivencias fueron reconstruidas después del episodio. Tampoco se diferenciaron las experiencias según el subtipo motor de delirium, lo que podría influir en la variabilidad de ciertas manifestaciones corporales y perceptuales.

En términos teóricos, el análisis se desarrolló bajo el marco de la cognición corporeizada y la circularidad cuerpo vivo–cuerpo vivido. No obstante, el estudio no incorporó mediciones fisiológicas simultáneas que permitieran examinar de manera directa la relación entre variaciones corporales y transformaciones perceptuales. La

ausencia de triangulación con indicadores del cuerpo vivo (como variabilidad cardíaca, potenciales evocados cardíacos, pupila o actividad EEG) limitó la articulación empírica entre los niveles fisiológicos, perceptivos y experienciales.

En términos metodológicos, el diseño cualitativo se aplicó en un único hospital, lo que restringe la transferibilidad de los resultados a otros contextos clínicos. La falta de registros en tiempo real (diarios, observación directa, apoyo audiovisual o tecnologías móviles) impidió documentar la secuencia temporal del episodio durante su desarrollo. Asimismo, no fue posible controlar de manera completa variables clínicas como sedación, interrupciones del sueño o fluctuaciones hemodinámicas, las cuales pueden incidir en la expresión del delirium o SSD.

PROPUESTAS DE FUTURAS INVESTIGACIONES

Los resultados de esta tesis, junto con las limitaciones metodológicas y teóricas identificadas, permiten delinear diversas líneas de investigación que podrían ampliar y profundizar la comprensión de la integración cuerpo–cerebro y la experiencia del delirium asociado a sepsis. A continuación, se describen las áreas propuestas:

- Desarrollo de estudios mixtos que integren, durante el mismo período clínico del delirium, registros fisiológicos (cuerpo vivo), evaluaciones conductuales estandarizadas y descripciones narrativas del cuerpo vivido. Esta integración, realizada en ventanas temporales coordinadas más que estrictamente simultáneas, permitiría examinar con mayor precisión las relaciones entre la dinámica autonómica, la actividad cortical, las manifestaciones conductuales y la experiencia corporal percibida durante el delirium (Halcomb & Hickman, 2015).

- Registros autonómicos (como presión arterial, dinámica pupilar, etc) con mayor tiempo de registro, que permitan estudiar la trayectoria de los cambios en el SNA a lo largo del episodio clínico (Shaffer & Ginsberg, 2017). Para reducir sesgos clínicos (asociados a variables de confusión como dolor, fatiga, disnea, fármacos y marcadores inflamatorios) y sesgos de subjetividad (derivados de la variabilidad en la evaluación clínica y conductual), estos estudios deberían integrar información clínica relevante, junto con variables que modulan la expresión del delirium, tales como fármacos con efecto sobre el sistema nervioso central o autónomo y marcadores inflamatorios sistémicos (Maldonado, 2018).
- La integración de registros cualitativos y conductuales durante el periodo activo del delirium es fundamental para comprender cómo se articulan los cambios fisiológicos con la vivencia subjetiva del episodio. La incorporación de perspectivas micro-fenomenológicas (Petitmengin, 2006), así como técnicas como diarios con apoyo familiar (Ullman et al., 2015), mapeos corporales (Coetzee et al., 2019). A nivel conductual, observación estructurada (Given, 2008), uso de dispositivos de registro en tiempo real (por ejemplo, acelerómetros (Yang & Hsu, 2010) o Mobile Brain/Body Imaging (Grasso-Cladera et al., 2022; Makeig et al., 2009; Stangl et al., 2023), permitiría documentar la evolución de la experiencia y su correspondencia con patrones conductuales y/ neuro-fisiológicos, evitando depender exclusivamente de reconstrucciones retrospectivas.
- Evaluación de la interocepción durante la fase aguda y en el seguimiento. La incorporación de tareas de percepción cardíaca u otras medidas interoceptivas posibilitaría explorar sus variaciones en relación con los HEP

(Coll et al., 2020; Engelen et al., 2023), con la organización cognitiva y perceptual del episodio. Este enfoque permitiría examinar la trayectoria de la integración viscero-cerebral y orientar el monitoreo y cuidado durante y después del delirium.

- Incorporación de estudios observaciones comparativo con múltiples grupos control diferenciados (Manterola et al., 2023), entre ellos personas sin patología, pacientes sépticos sin delirium y, pacientes sépticos con delirium. Esto permitiría distinguir con mayor claridad los efectos relacionados con la sepsis, con el delirium o con la interacción entre ambos.
- Caracterización de los hallazgos fisiológicos debería integrarse con los subtipos motores del delirium, los cuales se han asociado a patrones diferenciales de motricidad: hipoactivo, hiperactivo y mixto (la Cour et al., 2022). Esto podría reflejar mecanismos neurofisiológicos distintos. La integración entre estas presentaciones clínicas, los indicadores fisiológicos y las variaciones experienciales permitiría identificar perfiles más específicos del trastorno y profundizar en la comprensión de su heterogeneidad.

En conjunto, estas líneas de investigación permiten avanzar hacia un estudio más integrado de los procesos neuro-fisiológicos, conductuales y experienciales implicados en el delirium, considerando su carácter dinámico y su expresión en distintos niveles de organización.

VI. ASPECTOS ÉTICOS

La tesis se desarrolló en una población altamente vulnerable (pacientes con sepsis, con fluctuaciones de conciencia y capacidad decisional variable), lo que exigió resguardos éticos reforzados. Todos los estudios fueron aprobados por el Comité Científico–Ético institucional del Hospital Clínico de la Universidad de Chile (N.º 071/2023), el 19 de octubre de 2023, e implementaron medidas específicas para asegurar los principios de autonomía, bienestar y justicia.

Se aplicó consentimiento informado otorgado por representantes legales cuando los pacientes no estaban en condiciones de decidir, complementado con asentimiento verbal cuando fue posible. Durante los registros fisiológicos, se priorizó minimizar la interferencia con el cuidado clínico, evitar sobrecarga sensorial y detener las mediciones ante cualquier signo de fatiga, dolor o incomodidad.

En el estudio cualitativo, se adoptó una aproximación sensible y respetuosa: las entrevistas se realizaron en un ambiente protegido, se permitió al paciente pausar o detener la conversación cuando lo necesitara, y se prestó especial atención a posibles reacciones emocionales derivadas de relatar experiencias confusas o angustiantes. La confidencialidad se resguardó mediante codificación anónima y manejo seguro de datos.

Los principios de beneficencia, no maleficencia, autonomía y justicia guiaron todo el proceso. Se evitó cualquier procedimiento no clínico que implica riesgo adicional y se garantizó que la participación no afectara la atención médica habitual. Además, en los casos en que los pacientes presentaron delirium o SSD, se incluyó una acción de apoyo posterior a los registros: se brindó educación a la familia acerca del delirium y se entregó a los pacientes material de estimulación cognitiva,

acompañado de sugerencias personalizadas, con el fin de favorecer la orientación, el bienestar y la recuperación cognitiva temprana.

Estos resguardos fueron especialmente relevantes dado el interés de la tesis en procesos corporales y experienciales, donde la relación cuerpo–cerebro–mundo se encuentra especialmente vulnerable durante la enfermedad crítica.

VII. PALABRAS FINALES

El proceso doctoral trajo consigo una serie de desafíos que han ido marcando mi camino académico. Integrar nuevas perspectivas epistémicas y metodológicas (especialmente aquellas vinculadas a la cognición corporeizada) me obligó a repensar cómo planificar y llevar a cabo una investigación en contextos clínicos complejos. Esto no solo amplió mi manera de entender los fenómenos que estudiaba, sino también la forma de acercarme a ellos desde la investigación.

Uno de los primeros desafíos fue definir qué análisis eran realmente pertinentes para conectar las ideas teóricas con los datos que podía obtener. Aprender a identificar qué técnicas podían captar aspectos encarnados de la cognición y cuáles ofrecían información útil para entender la relación cuerpo–cerebro en el delirium, fue un proceso de constante ajuste y reflexión.

También debí tomar decisiones prácticas sobre cómo armar los registros y qué protocolos usar. Trabajar en entornos clínicos, especialmente con pacientes críticos, implica adaptarse: al equipamiento disponible, al tiempo real que dan las condiciones médicas, al personal con el que se cuenta y a los recursos económicos posibles. Donde se tomaron decisiones que integraran lo ideal y lo factible.

Otro aspecto fundamental fue el trabajo en equipo. Cada artículo que forma parte de esta tesis se construyó gracias a la colaboración con investigadores de distintas

áreas e instituciones. Participaron estudiantes, terapeutas ocupacionales, psicólogos, sociólogos, anestesistas y neurocientíficos. Cada uno aportó desde su mirada y experiencia, y siento que esa diversidad enriqueció el proceso y los resultados.

Finalmente, durante todo este camino traté de mantener una producción científica constante, no solo vinculada directamente al doctorado, sino también a proyectos y reflexiones que ya venía desarrollando previamente. Publicaciones, congresos y colaboraciones fueron parte de un mismo movimiento de aprendizaje continuo que acompañó mi formación doctoral.

VIII. REFERENCIAS

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IX. ANEXOS

A. Publicaciones generadas asociadas a asignaturas del Programa Doctoral

- **Álvarez, E. A., & Parada, F. J. (2021).**

  Association of pain during the evaluation of delirium in intensive care unit patients. **Frontiers in Medicine, 8:722001.**

  https://doi.org/10.3389/fmed.2021.722001 *(Revista Q1)*

- **Álvarez, E., & Gutiérrez, P. (2022).**

  Discurso y micropoder en la intervención con personas mayores con delirium hospitalizadas: reflexión en torno a las narrativas ausentes. **Cadernos Brasileiros de Terapia Ocupacional, 30.**

  https://doi.org/10.1590/2526-8910.ctoARF240431373 *(Revista Q3)*

B. Participación en congresos, seminarios y actividades académicas

2020

- Noviembre. **38º Congreso Chileno de Medicina Intensiva.**

  Revisando nuestras prácticas en delirium hiperactivo.

  Expositora invitada | Chile.

- Noviembre. **XXIV Congreso de la Sociedad de Geriatría y Gerontología de Chile.**

  Mesa *Delirium: importancia del tamizaje y diagnóstico*.

  Confusion Assessment Method. Expositora experta | Chile.

2021

- Mayo. **Congreso de Otoño – Sociedad Chilena de Medicina Intensiva.**

  Mesa *Hot Topics: Mujeres en UCI.* Expositora invitada | Chile.
- Noviembre. **15th Annual Meeting of the European Delirium Association.**

  Occupational therapy and delirium.

  Expositora internacional | Mesa Geriatric Care.
- Noviembre. **XXIX Congreso Chileno de Medicina Intensiva.**

  Reflexiones y perspectivas del proceso de investigación.

  Expositora invitada | Chile.

2022

- Marzo. **II Simposio Latinoamericano – American Delirium Society (Capítulo Latinoamericano).**

  Terapia ocupacional y delirium.

  Expositora invitada por reconocimiento internacional.
- Congreso de Otoño. **Sociedad Chilena de Medicina Intensiva.**

  Rol del terapeuta en la prevención del delirium post-pandemia.

  Expositora invitada | Chile.

2023

- Octubre (13/10). **Cutting Gardens Seminar.**

  Long-range temporal correlations in brain–heart of septic patients with delirium.

  Presentación oral | Chile.

- Noviembre (16/11). **Grupo de Oscilaciones – Workshop.**

  Is delirium in septic patients characterized by aberrant neuronal and heart-rate fluctuations?

  Presentación oral | University of Glasgow, Escocia.

2024

- Mayo. **American Thoracic Society (ATS) International Conference.**

  Mesa *State of the Science on ICU Delirium*.

  Rethinking non-pharmacologic prevention and treatment for ICU delirium.

  Investigadora invitada internacional | San Diego, EE. UU.
- Agosto. **XVI Congreso Chileno de Fisiatría.**

  De la idea al FONIS: experiencias con ECCR de alto impacto.

  Invitada | Mesa Investigación y Rehabilitación | Chile.
- Septiembre (27/09). **Jornada de Actualización de Enfermería Intensiva.**

  Prevención y manejo del delirium en el paciente crítico.

  Conferencista | Chile.
- Septiembre (27/09). **Jornada de Actualización de Enfermería Intensiva.**

  Síndrome post-UCI: perspectiva e impacto del equipo de enfermería.

  Conferencista | Chile.
- Octubre (24/10). **Congreso Latinoamericano de Terapia Ocupacional (CLATO).**

  Prevención no farmacológica del delirium postoperatorio por equipos de terapia ocupacional.

  Presentación oral | Perú.

- Octubre (25/10). **Congreso Latinoamericano de Terapia Ocupacional (CLATO).**

  Cambios en las actividades de la vida diaria en personas hospitalizadas por COVID-19 que presentaron delirium en UCI.

  Presentación oral | Perú.

2025

- Junio. **Organization for Human Brain Mapping (OHBM).**

  Mentoring Programme (selección mundial).

  Presentación de póster: *EEG Microstates in Septic Patients with Symptoms of Delirium.*

- Noviembre. **43º Congreso Chileno de Medicina Intensiva.**

  Trabajo interdisciplinar: integrando tecnología y evidencia para la prevención del delirium.

  Expositora invitada | Chile.

C. Premios y reconocimientos

- **2021 – Noviembre.**

  39º Congreso Nacional de Medicina Intensiva.

  Premio a profesional destacada a nivel nacional por contribución a la Sociedad Chilena de Medicina Intensiva.

- **2025- Mayo.**

  Colegio Chileno de Terapeutas Ocupacionales.

  Reconocimiento a terapeuta ocupacional destacada por aporte al desarrollo disciplinar.

D. Otras publicaciones

2020

- Pozzi, C., Tatzer, V. C., Álvarez, E. A., et al. (2020).
  The applicability and feasibility of occupational therapy in delirium care.
  European Geriatric Medicine, 11, 209–216.
  https://doi.org/10.1007/s41999-020-00308-z
  (Revista Q3)
- Garrido, M., Álvarez, E., Acevedo, P., et al. (2020).
  Early non-invasive brain stimulation with modified constraint-induced movement therapy for motor and functional upper limb recovery in stroke patients: Study protocol. British Journal of Occupational Therapy.
  https://doi.org/10.1177/0308022620904339
  (Revista Q2)

2021

- Garrido, M. A., Álvarez, E. A., Ponce, D. P., et al. (2021).
  *Consolidated framework for advancing implementation science for the implementation process and adherence assessment of a non-pharmacological delirium prevention program.*International Journal of Geriatric Psychiatry, 36(2), 302–313.
  https://doi.org/10.1002/gps.5425
  (Revista Q1)

2022

- Garrido, M., Álvarez, E., Acevedo, P., et al. (2022).
  *Early transcranial direct current stimulation with modified constraint-induced movement therapy for motor and functional upper limb recovery in hospitalized patients with stroke.*Brain Stimulation, 16(1), 40–47.
  https://doi.org/10.1016/j.brs.2022.12.008
  (Revista Q1)

2023

- Garrido, M., Álvarez, E., Salech, F., et al. (2023).
  *Software-guided (PREVEDEL) cognitive stimulation to prevent delirium in hospitalised older adults: Study protocol.*BMC Geriatrics, 23, 472.
  https://doi.org/10.1186/s12877-023-04189-2
  (Revista Q1)
- Álvarez, E., Garrido, M., Salech, F., et al. (2023).
  Early occupational therapy in mechanically ventilated patients improves functional status: Study protocol. British Journal of Occupational Therapy.
  https://doi.org/10.1177/03080226231184992
  (Revista Q2)
- Álvarez, E. A., Rojas, V. A., Caipo, L. I., et al. (2023).
  Non-pharmacological prevention of postoperative delirium by occupational therapy teams: A randomized clinical trial. Frontiers in Medicine, 10:1099594.
  https://doi.org/10.3389/fmed.2023.1099594
  (Revista Q1)

- Validez de instrumentos neuropsicológicos utilizados en el sistema de salud público chileno. (2023). Neuropsicología Latinoamericana, 15(3). https://neuropsicolatina.org/index.php/Neuropsicologia_Latinoamericana/article/view/833

E. Informes técnicos y guías

- **2024.**

  Toledo-Rodríguez, L., Casanova-Román, M., Álvarez-Espinoza, E., Delgado-Derio, C., Vallejos-González, J., Larenas-Rosa, D., Rivera-Lillo, G., Manzur-Valdivia, H., & Salas-Riquelme, C. (2024). *Rehabilitación en personas tras un ataque cerebrovascular (ACV): hacia dónde debemos avanzar.* Policy Brief. Universidad de Chile. Informe técnico nacional https://uchile.cl/dam/jcr:7854d944-e662-4fb1-8e60-55550de7ce8a/policy-brief-octubre-2025.pdf

- **2024.**

  Ferrante, L. E., Chaudhuri, D., Carayannopoulos, K. L., Jain, S., Tate, J. A., Álvarez, E. A., et al. (2024). *SCCM Guidelines on Caring for Older Adults in the Intensive Care Unit.* Society of Critical Care Medicine (SCCM). Guía clínica internacional . Rol: participación como coautora experta internacional en terapia ocupacional y envejecimiento, contribuyendo desde la perspectiva de rehabilitación, cuidado centrado en la persona y prevención de complicaciones cognitivas en adultos mayores críticos.