Programa de doctorado en Deporte y Salud

EFECTO AGUDO Y CRÓNICO DEL EJERCICIO DE ALTA INTENSIDAD EN LA FUNCIÓN COGNITIVA

Tesis Doctoral

Presentada por

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INFORMAN:

Que D. *Juan Arturo Ballester Ferrer* ha realizado bajo nuestra supervisión el trabajo titulado *"Efecto agudo y crónico del ejercicio de alta intensidad en la función cognitiva"* conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

Lo que firmo para los efectos oportunos,

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Director	Codirector
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Que D. *Juan Arturo Ballester Ferrer* ha realizado bajo la supervisión de nuestro Programa de Doctorado el trabajo titulado *"Efecto agudo y crónico del ejercicio de alta intensidad en la función cognitiva"* conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

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Para la realización del presente trabajo, titulado *“Efecto agudo y crónico del ejercicio de alta intensidad en la función cognitiva”*, el doctorando Juan Arturo Ballester Ferrer contó con la beca de investigación predoctoral que se nombra a continuación:

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Lista de abreviaturas

ADN: ácido desoxirribonucleico

ANOVA: análisis de la varianza

ANOVA RM: análisis de la varianza de medidas repetidas

BDNF: *brain derived neurotrophic factor*

CO_2: dióxido de carbono

CRT: *choice reaction time*

CSB: *corsi span backward*

CSF: *corsi span forward*

FC: frecuencia cardiaca

FC_{max}: frecuencia cardiaca máxima

FE: función ejecutiva

HIFT: *high intensity functional training*

HIIT: *high intensity interval training*

ICC: *intraclass correlation coefficient*

IGF-1: *insulin-like growth factor 1*

InT: *interference time*

LTRIMP: *lucia´s training impulse*

Met: metionina

MICT: *moderate intensity continuous training*

O_2: oxígeno

PCR: *polymerase chain reaction*

RPE: *rate of perceived exertion*

SNC: sistema nervioso central

SNP: *single nucleotide polymorphism*

TrT: *training test*

TSB: *total score backward*

TSF: *total score forward*

Val: valina

VAM: velocidad aeróbica máxima

VEGF: *vascular endothelial growth factor*

VO_2: consumo de oxígeno

VO_{2max}: consume máximo de oxígeno

VT1: *ventilatory threshold 1*

VT2: *ventilatory threshold 2*

Δ: *delta score*

η_p^2: eta parcial al cuadrado

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Resumen

Se ha demostrado que la función cognitiva y el bienestar psicológico, factores importantes en la salud mental de la población, pueden mejorar con el ejercicio físico a nivel agudo y crónico. Sin embargo, existe una gran heterogeneidad en cuanto a la magnitud de los resultados desconociéndose las características óptimas de las sesiones o los programas de ejercicio para provocar estos efectos, así como los moderadores y mecanismos potenciales que pueden estar contribuyendo. Por ello, el principal objetivo de la presente tesis doctoral fue analizar el efecto agudo y crónico del ejercicio físico en la función cognitiva y el bienestar psicológico de jóvenes estudiantes universitarios, desde una perspectiva que contemplara el lactato liberado (como medida de la intensidad del ejercicio), el polimorfismo genético de BDNF y el propio bienestar psicológico como potenciales mecanismos neurobiológicos y conductuales que pueden subyacer los efectos del ejercicio en la función cognitiva de jóvenes estudiantes universitarios. En una primera investigación (*estudio crónico)* se planteó un programa de entrenamiento funcional de alta intensidad (HIFT) de 10 semanas para ver su influencia en la velocidad de procesamiento, como medida de la función cognitiva, y en el estado afectivo y la vitalidad subjetiva, como medidas del bienestar psicológico. En un segundo estudio (*estudio agudo 1)* se valoró la influencia de diferentes intensidades de ejercicio como son el ejercicio moderado (MICT) y el ejercicio interválico de alta intensidad (HIIT) en la velocidad de procesamiento, el bienestar psicológico (siguiendo la línea del primer estudio, pero en este caso a nivel agudo) y, además, en una variable cognitiva más compleja

como es el control inhibitorio, estudiando el lactato asociado, el polimorfismo genético de BDNF y el bienestar psicológico como potenciales mecanismos subyacentes de la respuesta cognitiva. En un último estudio (*estudio agudo 2)* se centró la atención en aquellas variables cognitivas específicamente dependientes del hipocampo como son las relacionadas con la memoria, con una perspectiva basada en los potenciales mecanismos neurobiológicos (lactato y polimorfismo de BDNF). Los principales resultados obtenidos mostraron que el ejercicio de alta intensidad puede lograr resultados positivos en las diferentes dimensiones de la función cognitiva, tanto a nivel agudo, en mayor medida que MICT, como crónico. Respecto al bienestar psicológico, parece existir un impacto positivo del ejercicio a nivel agudo, tanto con el HIIT como el MICT, aunque MICT podría tener un impacto superior en este cometido. Sin embargo, no pudimos corroborar mejoras en el bienestar a nivel crónico tras el programa HIFT. En cuanto a los posibles mecanismos subyacentes en las mejoras cognitivas, analizados a nivel agudo, observamos relaciones entre los cambios cognitivos y el lactato liberado con el ejercicio, desde un punto de vista neurobiológico, y también con algunos componentes del propio bienestar psicológico, desde un punto de vista psicosocial/conductual. Sin embargo, el polimorfismo de BDNF no pareció influir en los resultados cognitivos. Finalmente, se requiere de más investigaciones que analicen la respuesta cognitiva al ejercicio desde una perspectiva que contemple diferentes moderadores y mecanismos subyacentes responsables de dicha relación.

Abstract

It has been demonstrated that the cognitive function and the psychological well-being, that are considered essential factors in the mental health of the population, can improve with physical exercise at the acute and chronic levels. However, there is a significant heterogeneity regarding the magnitude of the results, and the optimal characteristics of sessions or exercise programs to induce these effects, as well as the moderators and potential mechanisms that may be contributing, remain unknown. Therefore, the main aim of this doctoral thesis was to analyse the acute and chronic effects of physical exercise on the cognitive function and the psychological well-being of young university students, considering el released lactate (as a measure of the exercise intensity), the genetic polymorphism of BDNF, and the psychological well-being itself, as potential neurobiological and behavioral mechanisms that may underlie the effects of exercise on the cognitive function of young university students. In an initial research (chronic study), a 10-week high intensity functional training (HIFT) program was planned to assess its influence in the processing speed, as a measure of the cognitive function, and in the affective state and subjective vitality, as measures of the psychological well-being. In a subsequent research, (acute study 1), the influence of different exercise intensities, such as moderate exercise (MICT) and the high-intensity interval training (HIIT) was assessed in the processing speed, the psychological well-being (following the approach of the first research, but in this case, at an acute level), and furthermore, in a more complex cognitive variable as it is the inhibitory control,

studying associated lactate levels, the genetic polymorphism of BDNF and the psychological well-being as potential underlying mechanisms of the cognitive response. In the last research (acute study 2), the focus was on cognitive variables specifically dependent on the hippocampus, as those related to memory, from a perspective based on the potential neurobiological mechanisms (lactate and BDNF polymorphism). The key findings of the research showed that high intensity exercise can achieve positive results in the different dimensions of the cognitive function, both at an acute level, to a greater extent than MICT, and at a chronic one. Regarding psychological well-being, there seems to be a positive impact of exercise at an acute level, both with HIIT and MICT, although MICT could have a greater impact in this assignment. However, improvements could not be confirmed in well-being at a chronic level following the HIFT program. Regarding potential underlying mechanisms in cognitive improvements, analysed at an acute level, relationships between cognitive changes and lactate released with exercise were observed, from a neurobiological point of view and also with some components from the psychological well-being itself, from a psychosocial/behavioral perspective. Nevertheless, the BDNF polymorphism did not seem to affect the cognitive results. Finally, there is a need for further research to analyse the cognitive response to exercise from a perspective that considers different moderators and underlying mechanisms responsible for this relationship.

CAPÍTULO 1

INTRODUCCIÓN GENERAL

Capítulo 1. Introducción general

1.1. Aprendizaje y función cognitiva

El aprendizaje es un proceso de orden superior que emerge del Sistema Nervioso Central (SNC) y se forma a través de la interacción de diferentes funciones cognitivas (Diamond, 2013). Estas funciones cognitivas se definen como el conjunto de procesos mentales que contribuyen a la percepción, la memoria, el intelecto y la acción (Donnelly et al., 2016). Todas ellas conforman una base fundamental sobre la cual se establece la salud mental, lo que incluye tanto el bienestar como el malestar psicológico (Gale et al., 2012). Además, estas funciones cognitivas se pueden entender como un continuo que va desde el procesamiento de la información básica hasta las tareas que requieren altos niveles de función ejecutiva (FE) (Lubans, Leahy, Mavilidi, & Valkenborghs, 2022). En un extremo, las tareas básicas de procesamiento de información requieren menos recursos y, por lo tanto, representan un nivel más bajo de función cognitiva (Colcombe & Kramer, 2003). En el otro extremo, las FE representan procesos cognitivos de orden superior que son fundamentales para la planificación, la resolución de problemas y el aprendizaje (Diamond, 2013). Las FE centrales incluyen el control inhibitorio, la memoria de trabajo y la flexibilidad cognitiva (Lubans et al., 2022). Se han utilizado una gran variedad de tests cognitivos en las investigaciones experimentales para medir tanto el control inhibitorio (p. ej., test de Flanker, test de Stroop, *go/no-go task*), como la memoria de trabajo (p. ej., *digit span test*, test de Corsi) o la flexibilidad cognitiva (p. ej., *Trail Making test*, S*witch task*) (Wade, Leahy, Lubans, Smith, & Duncan, 2020).

1.2. Ejercicio físico y función cognitiva en personas jóvenes

Se ha demostrado que estas habilidades cognitivas son necesarias a lo largo de la vida para el funcionamiento diario óptimo, el éxito académico y la empleabilidad (Diamond, 2013; Titz & Karbach, 2014). Por ello, las estrategias para su optimización han sido ampliamente exploradas en la literatura. En este sentido, el ejercicio físico se ha convertido en una de las herramientas más prometedoras para obtener efectos beneficiosos en la plasticidad neuronal y la cognición, tanto a nivel agudo (Y. K. Chang, Labban, Gapin, & Etnier, 2012; Moreau & Chou, 2019; Oberste et al., 2019; Pontifex et al., 2019; Verburgh, Königs, Scherder, & Oosterlaan, 2014) como crónico (Colcombe et al., 2006; Erickson et al., 2011; Falck, Davis, Best, Crockett, & Liu-Ambrose, 2019; Loprinzi, Frith, Edwards, Sng, & Ashpole, 2018; Stern et al., 2019). Sin embargo, a pesar de la gran cantidad de trabajos dentro de este tópico, recientemente se ha destacado la necesidad de realizar investigaciones en grupos de población menos estudiados, como son los adolescentes y los adultos jóvenes (Hötting & Röder, 2013; Stillman, Esteban-Cornejo, Brown, Bender, & Erickson, 2020). Hasta la fecha, la gran mayoría de trabajos publicados que han explorado la relación entre el ejercicio físico y la función cognitiva han sido en adultos mayores (Hötting & Röder, 2013; Stillman et al., 2020), dado que las sociedades industrializadas se enfrentan a un envejecimiento de la población cada vez más patente, generando la necesidad de identificar intervenciones exitosas para mantener y mejorar la función cognitiva durante la vejez (Hötting & Röder, 2013). Sin embargo, investigaciones recientes indican que la actividad física realizada en etapas tempranas y medianas de la edad adulta predice niveles iniciales de memoria más altos y ratios de perdida más bajos en las fases más avanzadas de la vida (Kraal et al., 2021), mejor conectividad cerebral funcional (Ai et al., 2022), e implican una reducción del riesgo de demencia (Najar et al., 2019). De esta forma, el ejercicio físico puede proporcionar ventajas en forma de "reserva", lo que contribuiría a preservar la función cognitiva en la vejez (Ai et al., 2022; Best, Dao, Churchill, & Cosco, 2020; M. Chang et al., 2010; Loprinzi et al., 2018; Moffitt, Belsky, Danese, Poulton, & Caspi, 2017; Tucker-Drob, 2019).

Por ello, parece importante aumentar la evidencia sobre ejercicio y cognición en etapas más tempranas de la vida, tanto por las implicaciones inmediatas que puede tener durante esta etapa, como por el posible efecto protector que puede tener en edades más avanzadas. En este sentido, se han encontrado resultados prometedores sobre la capacidad del ejercicio físico a la hora de potenciar la función cognitiva en personas jóvenes tanto a nivel agudo (Chu et al., 2017; Haverkamp et al., 2020; Loprinzi, Roig, Etnier, Tomporowski, & Voss, 2021) como crónico (Haverkamp et al., 2020; Loprinzi et al., 2018; Loprinzi, Roig, et al., 2021; Stern et al., 2019). Diversos estudios han observado como aquellos jóvenes con una mejor condición física (aptitud cardiorrespiratoria) presentan una mejor función cognitiva (Aberg et al., 2009; Luque-Casado, Zabala, Morales, Mateo-March, & Sanabria, 2013; Wang et al., 2015) y un mayor rendimiento académico (Gil-Espinosa, Cadenas-Sanchez, & Chillón, 2019; Redondo-Flórez, Ramos-Campo, & Clemente-Suárez, 2022; Santana et al., 2017). Estos cambios funcionales vendrían acompañados por cambios a nivel estructural, ya que se ha sugerido que las mejoras en la aptitud cardiorrespiratoria podrían contribuir positivamente al desarrollo de diferentes regiones cerebrales en jóvenes estudiantes y, de esta forma, afectar al rendimiento académico de forma positiva (Belcher et al., 2021; Esteban-Cornejo et al., 2017; Esteban-Cornejo et al., 2019).

En conclusión, es necesario seguir estudiando los efectos agudos y crónicos del ejercicio y la influencia de la condición física en la salud cerebral y la función cognitiva en jóvenes, no solo por sus beneficios inmediatos durante dicha etapa de la vida (p.ej. rendimiento académico), sino por sus posibles efectos a largo plazo en la preservación de la salud cognitiva y en la posible prevención de las enfermedades neurodegenerativas en edades avanzadas, pudiendo entenderlo como una etapa sensible para ello.

1.3. Mecanismos explicativos del efecto del ejercicio físico sobre la función cognitiva

Paralelamente al estudio de los prometedores efectos del ejercicio en la función cognitiva, en la literatura se han estudiado los diferentes mecanismos potenciales que pueden subyacer a dichos efectos (Lubans et al., 2022; Lubans et al., 2016; Stillman, Cohen, Lehman, & Erickson, 2016; Stillman et al., 2020). Siguiendo la propuesta de Stillman et al. (2016), podemos estructurar dichos mecanismos en tres niveles de análisis (Figura 1). Un primer nivel de cambios moleculares y celulares. Un segundo nivel de cambios estructurales y funcionales y un tercer nivel de cambios psicosociales y conductuales. En este sentido, los dos primeros niveles harían referencia a los cambios neurobiológicos producidos en el organismo.

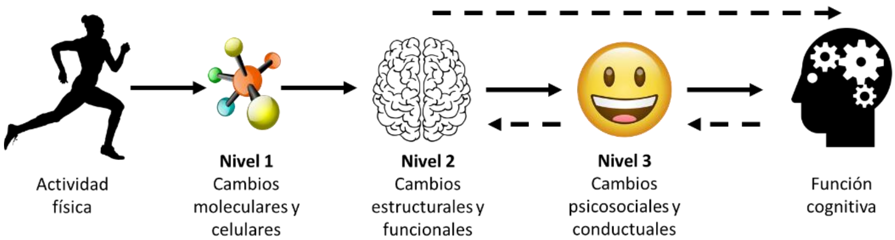

Figura *1. Mecanismos neurobiológicos (niveles 1 y 2) y psicosociales/conductuales (nivel 3) potencialmente responsables de los efectos cognitivos del ejercicio (adaptado de Stillman et al. (2016)).*

1.3.1. Mecanismos neurobiológicos (Niveles 1 y 2)

El primer nivel dentro de los mecanismos neurobiológicos engloba todos los cambios producidos a nivel microscópico (Nivel 1) (p. ej., celular y molecular) (Stillman et al., 2016). Desde este nivel, la expresión de genes con efectos neuroplásticos, como el Factor Neurotrófico Derivado del Cerebro (BDNF, por sus siglas en inglés), el Factor de Crecimiento del Endotelio Vascular (VEGF, por sus siglas en inglés) y el Factor de Crecimiento Similar a la Insulina Uno (IGF-1, por sus siglas en inglés), podrían subyacer los efectos positivos del ejercicio en la cognición (Fernandes, Arida, & Gomez-Pinilla, 2017; Voss, Vivar, Kramer, & van Praag, 2013; Wrann et al., 2013).

El segundo nivel trata los cambios producidos a nivel macroscópico (Nivel 2), los cuales están relacionados con los cambios en la estructura y función del cerebro y como esto puede estar explicando las mejoras cognitivas con el ejercicio (Stillman et al., 2016). Estos cambios de nivel 2 se han dividido, a su vez, en cambios en la estructura cerebral y cambios en la función cerebral. Los estudios centrados en la estructura cerebral indican cómo con el ejercicio pueden ocurrir cambios morfológicos en la materia gris y blanca, el grosor cortical y la integridad de la materia blanca del cerebro que puedan relacionarse con las mejoras cognitivas (Stillman et al., 2016; Stillman et al., 2020). Por otro lado, las investigaciones que han puesto su objetivo en los cambios en la función cerebral se han centrado en los cambios neuroeléctricos, medidos por resonancia magnética, en la activación funcional y la conectividad de cada región o entre las diferentes regiones del cerebro, como la corteza prefrontal o el hipocampo (Lubans et al., 2022; Stillman et al., 2016). Curiosamente, de todas estas estructuras el hipocampo ha sido aquella sobre la que existe mayor evidencia en relación a los cambios producidos con el ejercicio a nivel cerebral (Rendeiro & Rhodes, 2018). Este hecho es de gran importancia, puesto que se considera una estructura cerebral con un papel fundamental en la formación de la memoria, tanto la relacionada con los procesos de memoria declarativa (Squire et al., 1992), como con aquellos relacionados con la memoria visoespacial (El Hayek et al., 2019; Maguire et al., 1998).

1.3.2. Mecanismos psicosociales y conductuales (Nivel 3)

Por último, existe un conjunto de mecanismos psicosociales y conductuales que pueden estar explicando los efectos del ejercicio en la función cognitiva, conformando el tercer nivel propuesto por

Stillman et al. (2016). Por mecanismos psicosociales se entiende a aquellos estados mentales y comportamientos de orden superior que pueden verse afectados por el ejercicio y, por lo tanto, contribuir a sus efectos saludables a nivel cerebral y en la cognición (Stillman et al., 2020). Por ejemplo, cambios en el estado de ánimo u otras variables relacionadas con la salud mental (p.ej. bienestar y malestar psicológico) o en otras variables conductuales como el sueño o las habilidades de autorregulación pueden actuar como mecanismos o mediadores de los efectos del ejercicio en la función cognitiva (Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016).

La mayoría de estudios se han centrado en proponer potenciales mecanismos neurobiológicos, no prestando tanta importancia a los psicosociales y conductuales, a pesar de sus prometedores resultados (Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016). Además, desde un punto de vista clínico, los cambios en el comportamiento humano son mucho más fáciles de observar que los mecanismos neurobiológicos, por lo que existe un valor práctico añadido de este tipo de mecanismos (Stillman et al., 2016). En este sentido, es plausible que la actividad física también pueda mejorar la cognición a través de cambios en una gran variedad de mecanismos psicosociales (Lubans et al., 2016). Por ejemplo, se ha sugerido que los cambios a corto y largo plazo en variables relacionadas con el estado de ánimo y la salud mental pueden actuar como mediadores del efecto de la actividad física en la función cognitiva (Lubans et al., 2022).

Desde este enfoque, existe evidencia de que el ejercicio físico podría mejorar una variable determinante de la salud mental como el bienestar psicológico (Cervelló et al., 2014; Lubans et al., 2016; Mandolesi et al., 2018). Al mismo tiempo, el bienestar psicológico es visto como un modulador del proceso de aprendizaje, con investigaciones previas destacando su papel central en el rendimiento académico de los jóvenes estudiantes (Garcia et al., 2015; Yu, Shek, & Zhu, 2017).

En esta línea, aunque la mayoría de estudios han documentado efectos del ejercicio en la función cognitiva o en el bienestar psicológico, por separado, estos dos conceptos deberían estudiarse paralelamente puesto que se influyen mutuamente (Mandolesi et al., 2018). Se ha visto como los estados emocionales influyen en la función cognitiva a través de circuitos cerebrales específicos que involucran áreas prefrontales y estructuras límbicas (Barbas, 2000). Además, algunos estudios han planteado la hipótesis de que el bajo rendimiento cognitivo podría afectar al bienestar psicológico, lo que podría generar problemas de salud mental en el presente o en el futuro (Leahy et al., 2020). Para abordar su estudio, aunque todavía no hay acuerdo sobre qué define el bienestar psicológico (Korhonen, Linnanmäki, & Aunio, 2014), han salido a la luz algunas perspectivas (Ryan, Huta, & Deci, 2013). La perspectiva hedónica interpreta el bienestar como la presencia de afecto positivo y la ausencia de afecto negativo. Desde esta perspectiva, los trabajos desarrollados en el ámbito académico, muestran una clara relación positiva entre el logro académico y los factores positivos del bienestar (Garcia et al., 2015; Serrano & Andreu, 2016), y una relación negativa entre el rendimiento académico y los factores negativos del bienestar (Serrano & Andreu, 2016). Existen otras perspectivas para el estudio del bienestar como la perspectiva eudaimónica, la cual asocia el bienestar con la capacidad de un individuo para experimentar y ejercitar su potencial humano para lograr un funcionamiento psicológico óptimo (Ryan et al., 2013).

1.5. Moderadores de los efectos cognitivos del ejercicio

Ya se ha mencionado que tanto el ejercicio físico agudo como crónico, a través de diferentes mecanismos potenciales, puede influir positivamente en la plasticidad cerebral y la función cognitiva. Sin embargo, en la literatura sobre ejercicio y cognición, se han mostrado resultados muy heterogéneos en cuanto a la magnitud de estos efectos (Herold, Müller, Gronwald, & Müller, 2019). En este sentido, existen diferentes aspectos cuantitativos y cualitativos que pueden estar moderando dichos efectos y explicando esta variabilidad (Lubans et al., 2022; Lubans et al., 2016). En primer lugar, la relación dosis-respuesta del ejercicio, tanto a nivel agudo como crónico, ha emergido como una posible variable moderadora de los efectos (Y. K. Chang et al., 2015; Y. K. Chang et al., 2012; Herold et al., 2019; Ludyga, Gerber, Pühse, Looser, & Kamijo, 2020; Oberste et al., 2019). A nivel agudo, estudios previos indican que cuando se introduce un intervalo de descanso después de la sesión de ejercicio aeróbico (latencia), las intensidades más altas (> 93% de la frecuencia cardíaca (FC)) podrían acarrear las mayores ganancias cognitivas (Y. K. Chang et al., 2012; Herold, Behrendt, Meißner, Müller, & Schega, 2022; Oberste et al., 2019). También a largo plazo, se ha visto como programas de ejercicio interválico de alta intensidad (HIIT, por sus siglas en inglés) podrían provocar mejoras crónicas frente a otros de carácter continuo e intensidad moderada (MICT, por sus siglas en inglés) (Mekari et al., 2020). Sin embargo, en una revisión más reciente (Moreau & Chou, 2019), aunque encontraron una mejor respuesta del ejercicio de alta intensidad en comparación con el reposo, no fue así cuando se comparó con el ejercicio de moderada intensidad. Por otro lado, también existen algunos estudios que han sugerido una relación en forma de U invertida entre la intensidad del ejercicio y la cognición. De acuerdo con esta teoría, los protocolos de ejercicio de intensidad moderada otorgaron la mejor respuesta cognitiva en lugar de aquellos que incorporaron ejercicio de intensidades más ligeras o más altas (Pontifex et al., 2019).

Además, siguiendo con la dosis de ejercicio, el volumen parece tener influencia en los resultados a nivel agudo, obteniendo las mejores respuestas en sesiones de ejercicio de unos 20 min de duración (Y. K. Chang et al., 2019; Li et al., 2022; Oberste et al., 2019). Sin embargo, cuando nos referimos a investigaciones crónicas, la duración del programa de ejercicio no parece actuar como moderador de los efectos (Leahy et al., 2020). Esto implica la necesidad de tener en cuenta que algunos de estos moderadores relativos a la carga de ejercicio pueden ser muy influyentes a la hora de analizar la respuesta cognitiva aguda y crónica al ejercicio.

Otro factor considerado como un importante moderador de los efectos cognitivos del ejercicio ha sido el sexo (Barha, Hsu, Ten Brinke, & Liu-Ambrose, 2019; Barha & Liu-Ambrose, 2020; Ludyga et al., 2020). En este sentido, existe controversia cuando se analiza la respuesta cognitiva propiamente dicha, con gran parte de estudios que han mostrado una mejor respuesta al ejercicio aeróbico en mujeres (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017; Colcombe & Kramer, 2003), mientras que otros han informado de una menor efectividad en las mejoras cognitivas en mujeres respecto a los hombres, así como diferentes relaciones dosis-respuesta (Ludyga et al., 2020). Así, los estudios, deberían de conseguir muestras equiparadas entre sexos para conseguir aumentar la evidencia al respecto.

Por último, cuando hablamos de moderadores y se analizan aquellos con incidencia a nivel agudo, otro aspecto relevante en la literatura ha sido el momento de aplicación del test cognitivo y la duración de esos efectos en el tiempo (Loprinzi, Roig, et al., 2021; Roig et al., 2016). En este sentido, la memoria se caracteriza por presentar varias fases, incluida la adquisición (codificación) el almacenamiento (consolidación) y la recuperación (Morris, 2006).

La codificación implica el propio procesamiento de la información, lo que conlleva convertir una señal externa al lenguaje bioquímico del SNC, que se almacenará para su posterior recuperación (Morris, 2006). A nivel neurofisiológico, dicha codificación supondría la creación de una "huella de memoria" que se compone de una red neuronal que representa la memoria (Loprinzi, Roig, et al., 2021). La consolidación de la memoria implicaría la estabilización de dicha huella de memoria, cuyos procesos se cree que ocurren en múltiples niveles, incluido el celular/sináptico (consolidación sináptica) y el nivel del sistema cerebral (consolidación del sistema, donde la huella es distribuida desde el hipocampo a las áreas neocorticales para el almacenamiento a largo plazo) (Dudai, Karni, & Born, 2015).

Una vez consolidada, la memoria se “almacena”, posiblemente dentro de las espinas dendríticas (Poo et al., 2016). La última fase implicaría que, tras el uso de alguna señal (estado mental interno o estímulo externo) o de forma espontánea, los recuerdos pueden recuperarse y, posteriormente, provocar un estado de reconsolidación (Alberini, 2011).

En este sentido, el ejercicio podría vincularse a las distintas fases del aprendizaje y la memoria, dependiendo del punto temporal de exposición al estímulo (Loprinzi, Roig, et al., 2021). Algunos estudios han sugerido que abordar la fase de consolidación de la memoria (realizar el ejercicio después de la codificación) podría ser la estrategia más beneficiosa para mejorar la memoria a través del ejercicio (Roig et al., 2016). En este sentido, el ejercicio podría alterar transitoriamente la disponibilidad de neurotrofinas como el BDNF (Skriver et al., 2014) durante la consolidación, lo que podría conducir a las mejoras producidas en la memoria a largo plazo. De hecho, el BDNF ha sido, probablemente, el factor más estudiado en la literatura como un potencial implicado en los aspectos que subyacen a las mejoras cognitivas con el ejercicio (Cotman, Berchtold, & Christie, 2007; Kandola, Hendrikse, Lucassen, & Yücel, 2016).

1.6. BDNF y función cognitiva

La codificación genética y expresión de las denominadas neurotrofinas ha sido uno de los focos de estudio más importantes dentro de la investigación en ejercicio y cognición. El BDNF es una proteína que actúa como factor de crecimiento dentro de la familia de las neurotrofinas asociadas al factor de crecimiento nervioso, cuyas funciones son las de estimular la neurogénesis, la supervivencia, crecimiento y diferenciación de las células del sistema nervioso (Kowiański et al., 2018; Szuhany, Bugatti, & Otto, 2015; van Praag, 2008; Walsh, Smith, Northey, Rattray, & Cherbuin, 2020). En este sentido, los niveles de BDNF podrían mediar los efectos del ejercicio en el cerebro y, por extensión, en la cognición (Cotman et al., 2007; Kandola et al., 2016). De este modo, se ha observado que los niveles de BDNF aumentan en respuesta a una única sesión de ejercicio (Ferris, Williams, & Shen, 2007; Saucedo Marquez, Vanaudenaerde, Troosters, & Wenderoth, 2015), pudiendo funcionar como un potencial mecanismo de tipo neurobiológico, tal y como se comentó previamente (Fernandes et al., 2017; Voss et al., 2013; Wrann et al., 2013).

Se sabe que la secreción de BDNF está regulada por el gen homónimo, que tiene un polimorfismo de un solo nucleótido (SNP, por sus siglas en inglés) denominado polimorfismo del gen SNP rs6262 o BDNF Val66Met. Dicho polimorfismo de BDNF sustituye una valina (Val) por metionina (Met) en el codón 66. Las personas pueden presentar dos SNP de valina (Val/Val), una valina y una metionina (Val/Met) o dos metioninas (Met/Met). En la literatura se ha visto como la codificación genética de BDNF de los sujetos puede afectar a la respuesta cognitiva individual al ejercicio (Canivet et al., 2015; Hopkins, Davis, Vantieghem, Whalen, & Bucci, 2012). De este modo, el polimorfismo exhibido por la metionina (Met/Met) reduciría la secreción de BDNF (Egan et al., 2003) y podría explicar la respuesta disminuida observada al ejercicio en términos de sus efectos sobre la memoria en portadores de Met/Met (Canivet et al., 2015; Hopkins et al., 2012). No obstante, existen hipótesis contradictorias sobre la relación entre la respuesta cognitiva al ejercicio y el polimorfismo de BDNF (de Las Heras et al., 2022). Por un lado, en esa línea existen estudios que han sugerido que portar el alelo Val podría suponer una ventaja para mejorar la respuesta cognitiva al ejercicio a través del aumento en la secreción de BDNF (Mang, Campbell, Ross, & Boyd, 2013). Sin embargo, otros estudios indican que no se debe descartar que aquellos portadores de las variantes que se presuponen menos favorables (alelo Met) podrían beneficiarse más de la exposición a altos niveles de ejercicio, compensando la posible desventaja genética en la secreción de BDNF (Moreau, Kirk, & Waldie, 2017). Dados estos resultados divergentes (de Las Heras et al., 2022), parece necesario avanzar en nuestra comprensión de las implicaciones de los SNP de BDNF con el fin de obtener una respuesta cognitiva individual.

Un último aspecto importante, a tener en cuenta, es que la liberación de BDNF, además de estar regulada por el polimorfismo genético codificante de la proteína como se ha comentado, parece ser dependiente de la intensidad del ejercicio, observando mayores liberaciones en las intensidades más altas (Ferris et al., 2007;

Saucedo Marquez et al., 2015). Algo interesante asociado a este hecho es que el aumento agudo de BDNF se ha asociado con el aumento de lactato liberado durante el ejercicio de alta intensidad (Ferris et al., 2007; Gibbons et al., 2023; Müller, Duderstadt, Lessmann, & Müller, 2020).

1.7. Lactato y función cognitiva

Estudios recientes han sugerido que el lactato liberado por el musculo esquelético durante el ejercicio físico de alta intensidad puede desempeñar un papel importante en la respuesta cognitiva aguda (Ferris et al., 2007; Hashimoto, Tsukamoto, Ando, & Ogoh, 2021; Hashimoto et al., 2018; Herold et al., 2022; Kujach et al., 2019; Skriver et al., 2014). Es relevante estudiar el efecto del lactato sobre el SNC y la respuesta cognitiva como un posible biomarcador de la relación dosis-respuesta entre el ejercicio físico y la función cognitiva.

1.7.1. Lactato como combustible neuronal

Estudios previos han observado como el ejercicio intenso de tipo HIIT puede facilitar la activación neuronal y los niveles de excitación, lo cual podría explicar las mejoras en la función cognitiva (Egner & Hirsch, 2005; McMorris, 2016; Tsukamoto et al., 2016). Esta activación neuronal requiere de un aumento en el aporte de energía debido al transporte de neurotransmisores e iones (Dalsgaard, Ide, Cai, Quistorff, & Secher, 2002), siendo el lactato, el combustible preferente de las neuronas (Kemppainen et al., 2005). Además, se ha visto como el aumento sostenido de lactato sistémico en respuesta al ejercicio intenso promueve el suministro de lactato como sustrato energético para satisfacer las demandas neuronales de energía a nivel agudo (Barros, 2013; Hu & Wilson, 1997; Smith et al., 2003). Por otro lado, el lactato facilitaría la actividad sináptica (Schurr, West, & Rigor, 1988), la formación de la memoria (Suzuki et al., 2011) y la plasticidad neuronal (Yang et al., 2014).

En conjunto, se ha sugerido que el aumento de la actividad neuronal y la regulación del sistema cerebrovascular y los estados redox en respuesta al ejercicio, puedan ser los responsables de la mejoras cerebrales producidas por el mismo (Hashimoto et al., 2021). Esto podría explicar la importancia del suministro de lactato proveniente del músculo esquelético y, en consecuencia, del ejercicio físico intenso para la función cerebral (Hashimoto et al., 2021).

1.7.2. Lactato como precursor de BDNF

Además de los mencionados efectos directos en el SNC que se han atribuido al lactato, también pueden existir una serie de posibles efectos indirectos que deben ser tenidos en cuenta. Ya se ha comentado previamente que el BDNF es uno de los marcadores que más se ha relacionado con las mejoras cognitivas con el ejercicio (Cotman et al., 2007; Kandola et al., 2016) y que el HIIT genera mayores niveles de BDNF que el MICT (Saucedo Marquez et al., 2015), mostrando una dependencia de la intensidad para producir su liberación. Así, en humanos se ha sugerido que la mejora en la memoria a corto plazo estaba relacionada con el aumento agudo de BDNF (Griffin et al., 2011), aumento que se ha correlacionado con el incremento en la concentración de lactato durante el ejercicio (Ferris et al., 2007; Gibbons et al., 2023; Müller et al., 2020), o incluso tras una infusión del mismo en reposo (Müller et al., 2020; Schiffer et al., 2011). En ratones se ha observado como el lactato inducido por el ejercicio puede cruzar la barrera hematoencefálica induciendo la expresión de BDNF en el hipocampo y mejorando el aprendizaje y la memoria (El Hayek et al., 2019; Siebenmann et al., 2021). El lactato, por lo tanto, se ha propuesto como una molécula clave en la salud cerebral y la mejora cognitiva observada tras del ejercicio físico, vinculándose a las vías moleculares relacionadas con la neurogénesis (Morland et al., 2017) y promovedoras de la supervivencia neuronal (Lev-Vachnish et al., 2019).

1.8. Marco teórico

En resumen, en la Figura 2 se muestra un modelo de estudio en el cual se recogen los principales moderadores y mecanismos mencionados (Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016), que pueden estar regulando y propiciando los cambios cognitivos en respuesta al ejercicio, a partir del cual se establece el marco teórico de la presente tesis doctoral.

En base a este marco teórico, las investigaciones deberían, en primer lugar, tener en cuenta el análisis de moderadores mencionado anteriormente en busca de reducir la heterogeneidad observada en la literatura y obtener los protocolos óptimos de ejercicio que provoquen las mejoras cognitivas. En segundo lugar, se debería enfocar el estudio proponiendo e involucrando diferentes potenciales mecanismos subyacentes en las mejoras, ya que es probable que sea el resultado de interacciones multifacéticas de mecanismos neurobiológicos, psicosociales y conductuales (Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016).

Por todo ello, el principal objetivo de la presente tesis doctoral fue analizar el efecto agudo y crónico de la intensidad del ejercicio en la función cognitiva y el bienestar psicológico (determinantes de la salud mental) de jóvenes estudiantes universitarios, desde una perspectiva que contemplara el lactato liberado, el polimorfismo genético de BDNF y el propio bienestar psicológico como potenciales mecanismos neurobiológicos y psicosociales/conductuales que pueden subyacer los efectos del ejercicio en la cognición de jóvenes estudiantes universitarios.

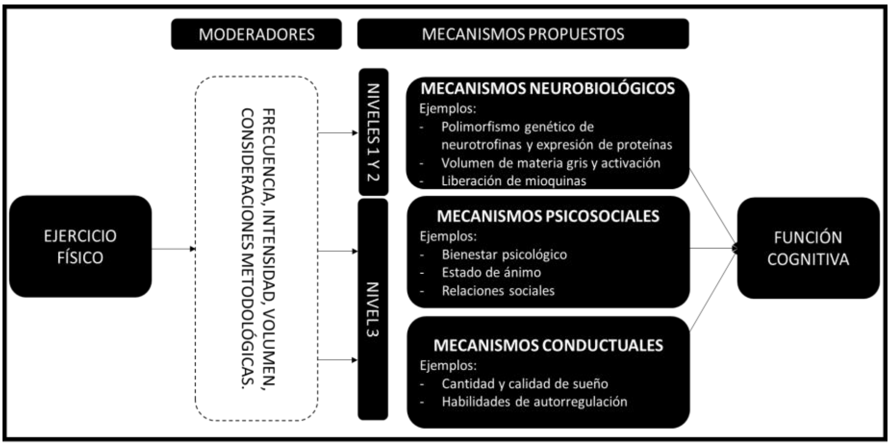

Figura 2: Moderadores y mecanismos responsables de los efectos del ejercicio físico en la función cognitiva (Adaptado de Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016).

CAPÍTULO 2

OBJETIVOS DE INVESTIGACIÓN E HIPÓTESIS

Capítulo 2. Objetivos de investigación e hipótesis

2.1. Objetivos generales

Con el fin de abordar la heterogeneidad en los resultados de la investigación sobre la relación entre ejercicio físico y función cognitiva que se ha mencionado en el apartado introductorio, se planteó un enfoque que contemplara algunos de los diferentes moderadores y mecanismos que pueden estar explicando dicha relación. Por ello, el principal objetivo de la presente tesis doctoral fue analizar el efecto agudo y crónico de la intensidad del ejercicio en la función cognitiva y el bienestar psicológico, proponiendo el lactato liberado, el polimorfismo genético de BDNF y el propio bienestar psicológico como potenciales mecanismos que pueden subyacer los efectos del ejercicio en la cognición (Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016).

Para lograr el objetivo principal se realizó un primer estudio (*estudio crónico*) donde se planteó un programa de entrenamiento funcional de alta intensidad (HIFT, por sus siglas en inglés) de 10 semanas, que presumiblemente lograría una gran adherencia al mismo en los participantes, con el objetivo inicial de comprobar si a la mejora de la condición física aeróbica tras el programa le acompañaría una mejora de la función cognitiva básica como es la velocidad de procesamiento (tiempos de reacción simple y complejos) y del bienestar psicológico. Sin embargo, este planteamiento inicial se tuvo que modificar como consecuencia del primer confinamiento en España por COVID-19. Por ello, se realizaron 5 semanas del protocolo original (entrenamiento presencial) y 5 semanas de entrenamiento online domiciliario. De este modo, el objetivo del proyecto original que intentaba relacionar las mejoras cognitivas y físicas no se pudo corroborar ya que, aunque si se valoró la cognición en estas circunstancias, no fue posible valorar la condición física post entrenamiento. Por ello, algunos objetivos fueron modificados dadas las circunstancias. Finalmente se intentó comprobar los efectos en la velocidad de procesamiento y el bienestar psicológico del HIFT en la cognición (a las 5 y a las 10 semanas) y como un periodo de cuarentena domiciliaria podría influir en ello. Adicionalmente, se valoró si existieron diferencias en la adherencia y la intensidad de las sesiones entre las 5 semanas de entrenamiento presencial y las 5 de entrenamiento online.

Como consecuencia de los resultados positivos observados en la cognición tras el programa de ejercicio de alta intensidad (de tipo HIFT), y en base a nuevas evidencias científicas que han observado en el lactato, metabolito característico de este tipo de programas de alta intensidad, como un potencial biomarcador involucrado en la respuesta cognitiva al ejercicio (Hashimoto et al., 2021; Hashimoto et al., 2018; Herold et al., 2022; Kujach et al., 2019; Skriver et al., 2014) se planteó un primer estudio de carácter agudo, siguiendo la línea del *estudio crónico*, para ver cómo podían influir diferentes intensidades de ejercicio, y el lactato asociado a las mismas, en la velocidad de procesamiento, el control inhibitorio y bienestar psicológico (*estudio agudo 1*). Por último, el *estudio agudo* 2 se centró específicamente en comprobar diferentes intensidades de ejercicio en aquellas variables de memoria dependientes del hipocampo (memoria visoespacial y memoria declarativa), dada la relación observada en modelos animales entre el lactato y la función del hipocampo. Además, en ambos estudios agudos se incluyó el polimorfismo genético de BDNF como otro posible moderador de los efectos.

Los títulos de los estudios comentados son los siguientes:

- *Estudio crónico: COVID-19 Quarantine Impact on Wellbeing and Cognitive Functioning During a 10-Week High-Intensity Functional Training Program in Young University Students*
- *Estudio agudo 1: Effect of acute exercise intensity on cognitive inhibition and well-being: Role of lactate and BDNF polymorphism in the dose-response relationship*
- *Estudio agudo 2: Memory Modulation by Exercise in Young Adults Is Related to Lactate and Not Affected by Sex or BDNF Polymorphism*

2.2. Objetivos específicos

Los objetivos específicos se han estructurado en función de los estudios incluidos en esta tesis doctoral:

2.2.1 Estudio crónico:

I. Analizar el efecto crónico de un programa de HIFT con dos fases (5 semanas de entrenamiento presencial y 5 semanas de entrenamiento online durante el confinamiento domiciliario por COVID-19) en la función cognitiva (velocidad de procesamiento) y el bienestar psicológico.

II. Valorar posibles diferencias en la adherencia y la intensidad de los entrenamientos entre las dos fases del programa (presencial frente a situación de confinamiento).

2.2.2 Estudio agudo 1:

III. Analizar el impacto agudo de la intensidad del ejercicio (HIIT frente a MICT) en la velocidad de procesamiento y el bienestar psicológico (siguiendo la línea del *estudio crónico*), además de una función más compleja, como el control inhibitorio (FE), fijando el volumen, considerado como óptimo, en 20 minutos (Y. K. Chang et al., 2019; Li et al., 2022; Oberste et al., 2019) y una latencia tras el ejercicio de 15 minutos que facilitaría los beneficios cognitivos y en el bienestar tras el ejercicio de alta intensidad (Y. K. Chang et al., 2012; Jung, Bourne, & Little, 2014; Malik, Williams, Weston, & Barker, 2019).

IV. Considerar posibles relaciones o influencias entre los cambios producidos en la cognición y posibles mecanismos propuestos desde un punto de vista neurobiológico y psicosocial/conductual (Lubans et al., 2016; Stillman et al., 2016), incluyendo el lactato sanguíneo, el polimorfismo genético de BDNF y el bienestar psicológico como potenciales mecanismos.

V. Comprobar, de forma paralela, el correcto funcionamiento de la app Test de Stroop UMH-MEMTRAIN para la valoración del control inhibitorio.

2.2.3 Estudio agudo 2:

VI. Comparar los efectos agudos del MICT frente al HIIT en aquellas funciones cognitivas dependientes del hipocampo (memoria visoespacial y declarativa) (El Hayek et al., 2019; Kandola et al., 2016; Maguire et al., 1998; Squire et al., 1992) desde la perspectiva neurobiológica dentro de los diferentes mecanismos potenciales (Lubans et al., 2016; Stillman et al., 2016).

VII. Estudiar las relaciones entre el lactato liberado, como posible mecanismo neurobiológico involucrado, y los cambios en la memoria, dado que de investigaciones previas se conoce que puede cruzar la barrera hematoencefálica y ser utilizado como sustrato a nivel cerebral (El Hayek et al., 2019; Hashimoto et al., 2018; Siebenmann et al., 2021), aumentando la producción de BDNF y mejorando la memoria en ratones (El Hayek et al., 2019).

VIII. Analizar la respuesta cognitiva al ejercicio de forma individual en función del polimorfismo genético de BDNF, dado que estas funciones mencionadas, dependientes del hipocampo, involucran de manera importante a BDNF (An, Li, Tang, Xu, & Sun, 2018; Bekinschtein, Cammarota, & Medina, 2014; Kandola et al., 2016), y se ha visto como el polimorfismo genético de dicha proteína (Val66Met) modula la secreción de la misma (Egan et al., 2003).

IX. Conocer la posible influencia del sexo en la respuesta cognitiva, ya que podrían existir diferencias en esta tras el ejercicio aeróbico (Barha et al., 2017; Colcombe & Kramer, 2003).

2.3. Hipótesis

Según las evidencias expuestas en el apartado introductorio de la presente tesis doctoral, se establecieron las siguientes hipótesis en los diferentes estudios:

2.3.1 Estudio crónico:

H1) El programa de HIFT produciría una mejora crónica de la función cognitiva (velocidad de procesamiento) (Loprinzi, Roig, et al., 2021; Stern et al., 2019).

H2) Los diferentes elementos del bienestar psicológico (vitalidad subjetiva y estado afectivo) se relacionarían entre sí (Cervelló et al., 2014).

H3) Se produciría una mejora general en el bienestar psicológico con el programa de entrenamiento, de forma paralela a las mejoras de la función cognitiva, presumiblemente a consecuencia de incrementos en la condición física (Eddolls et al., 2018).

H4) Se esperaría que todas las variables incluidas relacionadas con la salud mental (función cognitiva y bienestar psicológico) se vieran afectadas por el periodo de cuarentena estricta debido a COVID-19 (Brooks et al., 2020; Burke et al., 2020; Dragun et al., 2020). Por ello, esperamos que durante la segunda fase del programa (5 semanas de entrenamiento en cuarentena) se redujera la progresión de mejora de la función cognitiva y el bienestar psicológico respecto a la fase presencial del programa.

H5) Se producirían reducciones en la adherencia al programa durante la segunda fase del programa.

H6) La intensidad de entrenamiento podría ser mantenida durante la fase de entrenamiento domiciliaria, tras adaptar la programación a esta nueva situación.

2.3.2 Estudio agudo 1:

H7) El HIIT provocaría los mejores efectos, tras la latencia de 15 minutos, en velocidad de procesamiento, en línea con los resultados obtenidos en el *estudio crónico,* y control inhibitorio (FE), seguido del MICT y por último la situación control sin ejercicio (Y. K. Chang et al., 2012; Herold et al., 2022; Oberste et al., 2019).

H8) Los cambios producidos con el ejercicio en el lactato sanguíneo se relacionarían con los cambios cognitivos, tal y como se ha observado en investigaciones recientes (Ferris et al., 2007; Hashimoto et al., 2021; Hashimoto et al., 2018; Herold et al., 2022; Kujach et al., 2019; Skriver et al., 2014).

H9) Los sujetos con la codificación Val/Val presentarían mejores niveles de cognición a nivel basal y en respuesta a las modalidades de ejercicio propuestas respecto a aquellos con las variantes que incluyeran un alelo Met (Canivet et al., 2015; Egan et al., 2003; Hopkins et al., 2012).

H10) Tras la latencia de 15 minutos al terminar la sesión (Jung et al., 2014; Malik et al., 2019) el bienestar psicológico mejoraría de manera independiente de la intensidad del ejercicio (Cervelló et al., 2014).

H11) Los cambios cognitivos se relacionarían con cambios en las variables de bienestar psicológico, actuando como un potencial mecanismo de tipo psicosocial/conductual (Lubans et al., 2016; Stillman et al., 2016) vista previamente su potencial relación con el aprendizaje y la función cognitiva (Garcia et al., 2015; Leahy et al., 2020; Mandolesi et al., 2018; Yu et al., 2017).

H12) Respecto a la aplicación digital Test de Stroop UMH-MEMTRAIN (Pastor et al., 2018), esperaríamos encontrar resultados similares a los obtenidos por Y. K. Chang et al. (2019), donde la dificultad del test iría creciendo entre las diferentes condiciones (congruente, neutral e incongruente), siendo la última de las condiciones la que mayores tiempos de reacción y menores índices de precisión presentaría, indicando la validez de esta para la evaluación del control inhibitorio (Y. K. Chang et al., 2019; MacLeod, 1991; Milham et al., 2002)

2.3.3 Estudio agudo 2:

H13) Se obtendría una respuesta al ejercicio dependiente del lactato liberado durante el mismo en la memoria (El Hayek et al., 2019; Hashimoto et al., 2018; Siebenmann et al., 2021), siendo, por lo tanto, el HIIT superior al MICT en este cometido.

H14) Se esperaría una mejor respuesta del ejercicio sobre la memoria en los sujetos con la codificación Val/Val respecto a aquellos con la presencia del alelo Met (Val/Met y Met/Met), dada su importancia en la liberación de BDNF, factor íntimamente relacionado con la memoria (Canivet et al., 2015; Egan et al., 2003; Hopkins et al., 2012).

H15) Respecto al sexo, debería ocurrir una mayor respuesta aguda al ejercicio en las mujeres respecto a los hombres en la memoria (Barha et al., 2017; Colcombe & Kramer, 2003).

CAPÍTULO 3

RESUMEN DE LOS MÉTODOS

Capítulo 3. Resumen de los métodos.

3.1. Participantes

Todos los participantes incluidos en los estudios de la presente tesis fueron jóvenes estudiantes universitarios con un rango de edad entre los 18 y los 30 años. Los procedimientos experimentales siguieron la 7ª Declaración de Helsinki y fueron aprobados por el Comité de Ética de la Universidad (UMH.CID.DPC.02.17). Todos los participantes incluidos dieron su consentimiento informado, siendo informados por escrito de todas las características de la investigación, antes de participar en el estudio y fueron informados de la confidencialidad y anonimato de los resultados obtenidos. En cada uno de los estudios, se incluyen cálculos específicos relativos al tamaño muestral de cada uno de ellos.

3.2. Diseños Experimentales

Para el *estudio crónico* se dividió a los participantes, de forma aleatoria, en un grupo experimental de entrenamiento de HIFT y un grupo control sin entrenamiento. El protocolo experimental constó de 10 semanas, dividido en dos fases de 5 semanas (entrenamiento grupal supervisado y entrenamiento individual online durante la cuarentena por COVID-19 en marzo de 2020), realizando una medición de las variables de análisis al finalizar cada una de las fases.

En cuanto a los estudios agudos (*Estudios agudos 1 y 2*), en ambos se utilizó un diseño de medidas repetidas donde todos los participantes realizaron todas las condiciones experimentales contempladas en el protocolo de cada uno de los estudios. Para ello, se utilizó un orden aleatorizado y contrabalanceado entre los sujetos y las condiciones, valorando las medidas principales incluidas en cada estudio antes y después de cada una de las condiciones experimentales, las cuales se detallan en el apartado de procedimiento.

3.3. Procedimientos

3.3.1. *Estudio crónico*

Al inicio, todos los participantes completaron un test incremental para obtener su rendimiento cardiorrespiratorio y una familiarización con el test cognitivo (velocidad de procesamiento). Posteriormente se obtuvieron las medidas cognitivas y de bienestar psicológico pre-programa de entrenamiento. Las posteriores evaluaciones de ambas variables realizaron tras una primera fase de 5 semanas de entrenamiento grupal supervisado (marzo de 2020) (POST5), y tras 5 semanas de entrenamiento individual en casa durante el periodo de cuarentena por la pandemia mundial del COVID-19 (abril 2020) (POST10).

El programa de entrenamiento fue planificado, prescrito y supervisado por dos miembros del grupo de investigación. Las sesiones tuvieron una duración de una hora, tres días a la semana no consecutivos. La intervención presencial se llevó a cabo en las instalaciones de la universidad, mientras que las sesiones de entrenamiento durante la fase de cuarentena se enviaron a los participantes a través de una aplicación móvil para que se realizaran en casa.

Las sesiones se dividieron en cuatro partes: (a) 10 min de activación; (b) un bloque de fuerza de unos 15 min, ocasionalmente, sobre un patrón de movimiento específico con una carga relativa en función de las manifestaciones de resistencia muscular o hipertrofia, según la programación; (c) HIFT como bloque de entrenamiento principal, que varió de 10 a 30 min; y (d) 10 min de vuelta a la calma mediante ejercicios de movilidad y de estiramientos estáticos. En el bloque principal de HIFT se utilizaron métodos de repeticiones (completar una serie de ejercicios en el menor tiempo posible) o métodos de tiempo (ratios trabajo-descanso similar al método HIIT tradicional donde se debían realizar el máximo número de repeticiones durante el tiempo de trabajo). Por lo tanto, la intensidad requerida fue *all-out* para todas las sesiones, y la recuperación para el método de repeticiones fue a su propio ritmo, autoseleccionada y pasiva (Feito, Heinrich, Butcher, & Poston, 2018). Este bloque incluía ejercicios cíclicos, como correr o saltar a la comba, y ejercicios de resistencia muscular con peso corporal o cargas ligeras (p. ej., sentadillas, swings, lanzamientos de balón medicinal, flexiones, dominadas…) (Feito et al., 2018). Durante el segundo periodo de entrenamiento (fase de cuarentena), los entrenamientos se adaptaron a esta nueva situación. Así, se prescribió el trabajo con cargas utilizando materiales genéricos que cualquier persona puede tener en casa (sacos de arroz, botellas de agua, recipientes de leche y otros materiales comunes) (Jiménez-Pavón, Carbonell-Baeza, & Lavie, 2020), pidiendo que mantuvieran los criterios mencionados anteriormente.

La monitorización de la intensidad en las sesiones de entrenamiento presencial se realizó con dos métodos diferentes, uno objetivo y otro subjetivo: la FC y la escala de percepción subjetiva del esfuerzo (RPE, por sus siglas en inglés), respectivamente. Durante la cuarentena solamente se utilizó el RPE durante las sesiones. Con la FC registrada se calculó la carga de las sesiones en las sesiones presenciales, utilizando el método de Impulso de entrenamiento de Lucía (LTRIMP, por sus siglas en inglés) (Lucía, Hoyos, Carvajal, & Chicharro, 1999), que utiliza la FC en los umbrales ventilatorios individuales obtenidos en la prueba de esfuerzo para establecer tres zonas de entrenamiento: Zona 1 "por debajo del primer umbral ventilatorio (VT1, por sus siglas en inglés)", Zona 2 "entre VT1 y el segundo umbral ventilatorio (VT2, por sus siglas en inglés) " y Zona 3 "por encima de VT2". Para el cálculo del LTRIMP, el tiempo empleado en cada zona se multiplica por el número de zona (1, 2 o 3). Por otro lado, se utilizó la escala modificada de 10 puntos para cuantificar la carga interna a través del RPE (Foster et al., 2001). Se pidió a los participantes que determinaran la intensidad del entrenamiento a través de la escala 30 min después de completarlo.

3.3.2. *Estudio agudo 1*

Todos los participantes completaron tres condiciones experimentales (una sesión de HIIT, una sesión de MICT y una sesión control sin ejercicio), siguiendo un orden aleatorizado y contrabalanceado entre las condiciones, con una semana de diferencia. Antes de comenzar el protocolo experimental, los sujetos realizaron una fase de familiarización y entrenamiento del Test de Stroop, y una evaluación del rendimiento cardiorrespiratorio para prescribir las sesiones de ejercicio de manera individualizada. Además, también se tomaron muestras de saliva para el análisis genético. Todas las condiciones experimentales comenzaron a las 9:00 a.m.

Las sesiones experimentales (HIIT, MICT y control) tuvieron una duración de 20 min, puesto que parece el volumen óptimo de ejercicio para producir los efectos deseados en la cognición (Y. K. Chang et al., 2019; Li et al., 2022; Oberste et al., 2019). Antes de realizar cada una de las sesiones y 15 min tras la parte principal cada una de ellas, los participantes completaron el Test de Stroop y los cuestionarios de bienestar psicológico (vitalidad subjetiva y estado afectivo), siempre bajo las mismas condiciones. Las muestras de lactato sanguíneo se obtuvieron antes de cada condición, a los 3 y a los 15 min tras la finalización de la parte principal de las mismas, coincidiendo la última muestra con el comienzo la evaluación cognitiva, momento en el cual parecen maximizarse las ganancias cognitivas tras el ejercicio agudo (Y. K. Chang et al., 2012).

Respecto a las sesiones, para la condición control se pidió a los participantes que permanecieran sentados en reposo. Las condiciones de ejercicio se realizaron en cinta rodante y contaron con una activación de 3 min al 60% de la VAM. Para la sesión de MICT, se pidió a los participantes que mantuvieran dicha velocidad de carrera hasta completar la parte principal de la sesión. Por su parte, la sesión de HIIT consistió en 4 series de 2 min al 95% de la VAM con 2 min de recuperación pasiva entre series. Ambas sesiones de ejercicio finalizaron con un periodo de vuelta a la calma de 3 min, obteniendo finalmente la misma duración total (20 min) en las tres condiciones experimentales. La FC se controló utilizando sensores H7 y la aplicación Polar Beat (Polar Electro Oy, Kempele, Finlandia).

3.3.3. *Estudio agudo 2*

Al comienzo, los participantes completaron una prueba incremental de rendimiento para establecer la carga de trabajo individualizada durante la sesión de HIIT y la sesión de MICT. Por otro lado, se obtuvieron muestras de saliva para determinar el polimorfismo de BDNF y se explicó el funcionamiento del test de memoria visoespacial incluido en el protocolo. Posteriormente, se contrabalancearon las dos condiciones experimentales (MICT y HIIT) con, al menos, una semana de diferencia. Todas las sesiones comenzaron a las 9:00 a.m.

En las condiciones experimentales, la evaluación de la memoria visoespacial se llevó a cabo antes y después de cada una de ellas. La medida post sesión se administró 15 min tras el cese de la parte principal de la sesión, lo cual parece un lapso de tiempo óptimo para maximizar las ganancias (Y. K. Chang et al., 2012). Por otro lado, la tarea utilizada para evaluar la memoria declarativa a largo plazo se administró antes de cada una de las sesiones de ejercicio, situando la sesión de ejercicio durante la etapa de consolidación de la memoria (Loprinzi, Roig, et al., 2021), realizando la evaluación sobre dicha memoria declarativa a las 48 horas y los 7 días tras la realización de la sesión experimental.

Para las condiciones experimentales (HIIT y MICT) se estandarizó la duración de ambas en 20 min, debido a que podría ser un volumen óptimo para observar los efectos positivos agudos en la cognición (Y. K. Chang et al., 2019; Li et al., 2022; Oberste et al., 2019). Las sesiones se realizaron en cinta rodante y contaron con un calentamiento de 3 min al 60% de la VAM. Para la sesión de MICT, se pidió a los participantes que mantuvieran dicha velocidad de carrera hasta completar la duración establecida para la parte principal de ambas condiciones experimentales. Por otro lado, la sesión de HIIT consistió en 4 series de 2 min al 95% de la VAM con 2 min de recuperación pasiva entre series. Para finalizar se llevó a cabo un periodo de vuelta a la calma de 3 min. La FC se controló utilizando sensores H7 sincronizadas a tiempo real con la aplicación Polar Beat (Polar Electro Oy, Kempele, Finlandia). Las muestras de lactato en sangre se obtuvieron antes del inicio de cada condición y 3 y 15 min tras el cese de la parte principal de cada una de las condiciones de ejercicio, coincidiendo la última toma de lactato con el inicio de la evaluación cognitiva post ejercicio.

3.4. Mediciones

3.4.1. *Estudio crónico*

3.4.1.1. Función cardiorrespiratoria: Prueba de esfuerzo.

Los participantes del grupo experimental realizaron una prueba incremental máxima en una cinta rodante con una medida de consumo de oxígeno (VO_2) y de FC para determinar el VO_2 máximo (VO_{2max}), FC máxima (FC_{max}), y sus valores asociados en VT1 y VT2. El intercambio de gases respiratorios se midió mediante el analizador MasterScreen CPX (Hoechberg, Alemania) respiración a respiración después de ser calibrado. El $VO_{2máx}$ se calculó como la media más alta de VO_2 de 30 s. Además, se utilizaron medias de 15 s de O_2 y CO_2 para determinar VT1 y VT2 (Pettitt, Clark, Ebner, Sedgeman, & Murray, 2013). A los participantes no se les permitió beber ni hablar durante la prueba y se les pidió que se abstuvieran de hacer ejercicio intenso 24 horas antes. El protocolo de prueba incremental consistió en una entrada en calor de 3 min a 5 km/h con una pendiente del 1%. Luego, la prueba se realizó en una pendiente del 1% y comenzó a una velocidad de 6 km/h y aumentó 1 km/h por minuto hasta la fatiga. El protocolo de prueba incremental no se pudo repetir al final del estudio debido al confinamiento domiciliario por COVID-19, por lo que no se obtuvieron datos sobre las posibles mejoras en el estado físico de los participantes.

3.4.1.2. Función cognitiva: Velocidad de procesamiento

La función cognitiva se evaluó a través de una aplicación digital para smartphones (Pastor & Cervelló, 2019), la cual contemplaba tres pruebas para evaluar la velocidad de procesamiento, a través de diferentes tiempos de reacción. Cada prueba consistía en pasar diez pruebas de diferentes estímulos, y entre cada prueba, había un período de descanso aleatorio entre 1.000 y 1.500 ms. La primera prueba, la Prueba de Entrenamiento (TrT, por sus siglas en inglés), se utilizó para entrenar a los participantes al comienzo de cada medida. En el TrT se presentaba un estímulo luminoso verde o rojo, y el sujeto debía pulsar un botón verde sólo si el estímulo presentado era del mismo color. En la segunda prueba, la

Prueba de Reacción de Elección (CRT, por sus siglas en inglés) (ICC = 0.78, SEM = 0.05 s), también había dos señales luminosas, roja y verde, y dos botones, rojo y verde. El sujeto tenía que pulsar el botón con el color correspondiente a la señal luminosa presentada (por ejemplo, si la señal luminosa era roja, tenía que pulsar el botón rojo). La tercera prueba, la Prueba de Interferencia (InT, por sus siglas en inglés) (ICC = 0.80, SEM = 0.05 s), la más compleja, consistió en añadir interferencia en el proceso de decisión en relación a la segunda prueba: los participantes debían responder a la inversa, de manera que la señal no debía coincidir con el color del botón (por ejemplo, si la señal luminosa era verde, debían presionar el botón rojo). Se registraron los tiempos de reacción de cada una de las pruebas.

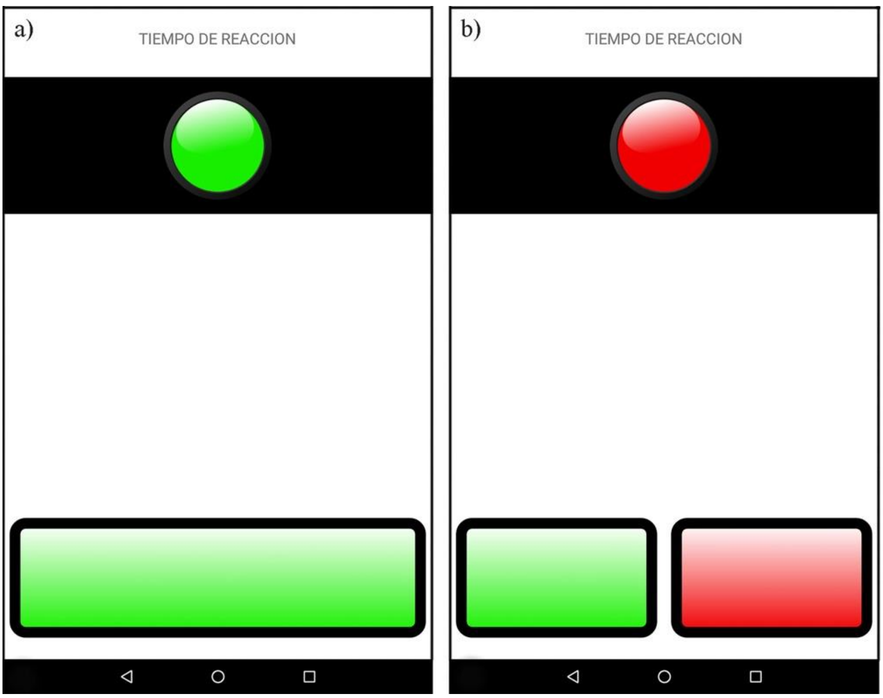

Figura 3. Tests de tiempo de reacción. (**a**) CRT; (**b**) InT.

3.4.1.3. Bienestar Psicológico

El bienestar psicológico se evaluó a través de cuestionarios sobre vitalidad subjetiva (Molina-García, Castillo, & Pablos, 2007; Ryan & Frederick, 1997; Ryan et al., 2013) y sobre estado afectivo positivo y negativo (Mackinnon et al., 1999). El instrumento sobre vitalidad subjetiva está compuesto por siete ítems que indican cómo se siente uno en el presente (p. ej., me siento vivo y vital). Las respuestas se califican en una escala tipo Likert de ocho puntos que va de 0 (*no es completamente cierto*) a 7 (*muy cierto*). El alfa de Cronbach en las diferentes situaciones experimentales estuvo comprendido entre 0.88 y 0.95. En cuanto a la escala para el estado afectivo, está compuesta por nueve adjetivos, los cuales se agrupan en dos factores en respuesta al ítem "Indica cómo te sientes en este momento…". Cuatro de sus ítems están asociados con *el Estado Afectivo Positivo* ("alegre, feliz, contento, divertido") y cinco con *el Estado Afectivo Negativo* ("deprimido, preocupado, frustrado, enojado, infeliz"). Las respuestas se califican en una escala tipo Likert de ocho puntos que va de 1 (*no completamente*) a 7 (*extremadamente*). El alfa de Cronbach para el Estado Afectivo Positivo estuvo entre 0.89 y 0.95, y para el Estado Afectivo Negativo entre 0.83 y 0.92. Estos datos, muestran una alta fiabilidad de los cuestionarios que midieron el bienestar psicológico (Nunnally, 1978).

3.4.1.4. Adherencia al programa de entrenamiento

Se monitorizó la participación, tanto en la fase de entrenamiento presencial como en la fase de entrenamiento en cuarentena. Se realizaron un total de 30 sesiones, 15 en cada una de las fases del programa (fases supervisadas y online). La adherencia se consideró suficiente si se completaba al menos el 90% de las sesiones (Heinrich, Patel, O'Neal, & Heinrich, 2014).

3.4.2. *Estudio agudo 1*

3.4.2.1. Prueba de rendimiento cardiorrespiratorio

Se realizó una prueba de ejercicio incremental hasta el agotamiento voluntario en cinta rodante para determinar la Velocidad Aeróbica Máxima (VAM) y la FC_{max}, con las que prescribir y cuantificar la carga de las sesiones. Durante la prueba, se monitorizó una medición de FC usando la banda pectoral polar H7 (Polar Electro Oy, Kempele, Finlandia). Después de un calentamiento de 3 min a 5 km/h, la velocidad se incrementó en 1 km/h cada minuto hasta el agotamiento. La cinta de correr se fijó a una pendiente del 1% tanto para el calentamiento como para la parte principal. A los participantes no se les permitió beber ni hablar durante la prueba y se les pidió que se abstuvieran de hacer ejercicio intenso durante las 24 horas previas a la prueba.

3.4.2.2. Función cognitiva

3.4.2.2.1. Test de Stroop

El test de Stroop (Stroop, 1935) es uno de los instrumentos neuropsicológicos más utilizados para evaluar varios procesos cognitivos centrales, incluida la FE, la velocidad de procesamiento, la atención selectiva y el control inhibitorio (Y. K. Chang et al., 2019; Y. K. Chang et al., 2015; Golden, 1994). Se utilizó una versión digital del test (Stroop test UMH-MEMTRAIN de Pastor et al., 2018), que permitió evaluar el tiempo de reacción y la precisión en las diferentes fases del test, siguiendo el protocolo original descrito por Golden (1994). La prueba consta de tres fases de dificultad creciente (congruente, neutral e incongruente). Cada condición tiene una duración de 45 s, donde se registra el número de respuestas correctas e incorrectas y el tiempo de reacción de las respuestas. La prueba hace una pausa de 25 s antes de iniciar la siguiente condición. El rendimiento en las pruebas congruente y neutral es una medida de la velocidad de procesamiento básica, mientras que la condición incongruente indica una medida del control inhibitorio (Y. K. Chang et al., 2019). En este sentido, en ambos puntos de medición, observamos diferencias en los tiempos de reacción ($p < 0.01$) y los índices de precisión ($p < 0.01$) entre las diferentes condiciones del test, siendo la condición incongruente la más compleja al respecto (mayores tiempos de reacción y peores índices de precisión), observando el típico efecto Stroop y, por ende, el correcto funcionamiento de la herramienta tanto para la valoración de la velocidad de procesamiento como del control inhibitorio (Y. K. Chang et al., 2019; MacLeod, 1991; Milham et al., 2002). En cuanto a la fiabilidad, encontramos coeficientes de correlación intraclase (ICC, por sus siglas en inglés) altos (> 0.70) (Rodríguez Barreto, Pineda Roa, & Pulido, 2016) para cada una de las condiciones del test (congruente = 0.76; neutral = 0.76; incongruente = 0.79).

Figura 4. Test de Stroop. **a**) Condición Congruente; **b**) Condición Neutra; **c**) Condición Incongruente.

3.4.2.3. Bienestar psicológico

Se evaluó el bienestar psicológico, además de la función cognitiva, con los mismos instrumentos que en el *estudio crónico* (vitalidad subjetiva y estado afectivo), descritos en el apartado *3.4.1.3*. En este caso, en relación a la vitalidad subjetiva, el alfa de Cronbach en las diferentes situaciones experimentales estuvo comprendido entre 0.76 y 0.92. En cuanto al estado afectivo (positivo y negativo), el alfa de Cronbach osciló entre 0.74 y 0.96 .

3.4.2.4. Lactato Sanguíneo

Para determinar las concentraciones de lactato se obtuvieron muestras de sangre del lóbulo de la oreja de los sujetos utilizando un analizador de lactato portátil (Lactate Scout, SensLab GmbH, Leipzig - Alemania).

3.4.2.5. Análisis genético

Las muestras de saliva, utilizadas para conocer el SNP de BDNF, se obtuvieron con un kit de recolección de saliva de ADN OrageneTM (DNA Genotek SL, Ottawa, ON, Canadá). El protocolo de extracción de ADN fue proporcionado por el fabricante. La muestra se analizó posteriormente mediante una PCR cuantitativa StepOne plus de Applied Biosystem (Thermo Fisher Scientific SA, Waltham, MA, EE. UU.), siguiendo el protocolo de Sánchez-Romero, Dorado, Guarino, and Llerena (2009).

3.4.3. Estudio agudo 2

3.4.3.1. Prueba de rendimiento cardiorrespiratorio

Se realizó una prueba de ejercicio incremental hasta el agotamiento voluntario en cinta rodante siguiendo el protocolo descrito previamente en el *estudio agudo 1* (*3.4.2.1).*

3.4.3.2. Función cognitiva

3.4.3.2.1. Memoria visoespacial

Una versión digital del Test de Corsi se utilizó para valorar la memoria visoespacial y la memoria de trabajo a corto plazo (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000; Wechsler, 2004). El protocolo contempla dos modalidades: hacia delante (*Forward*) y a la inversa (*Backward*) dentro de una misma tarea. Diez elementos son visibles en la pantalla, y para cada prueba estos elementos se "iluminan" uno por uno, a una velocidad de un elemento por segundo, en un orden aleatorio. La modalidad *Forward* requiere que los participantes toquen los elementos en el mismo orden en que aparecieron por primera vez en la pantalla, inmediatamente después de que se haya mostrado el último elemento de la secuencia. Para la modalidad *Backward*, en cambio, se indica a los participantes que repitan la secuencia en orden inverso. Los participantes tienen dos intentos por cada nivel con el mismo número de elementos. Si al menos uno de los intentos tiene éxito, se administra el siguiente nivel aumentando un elemento en la secuencia. La prueba termina una vez que el participante no logra replicar dos secuencias consecutivas del mismo nivel/longitud. Dadas las características del test, se obtienen varios tipos de puntuación para cada una de las modalidades: por un lado, el número de intentos exitosos logrados hasta el final de la prueba y, por otro lado, la longitud final obtenida en la última secuencia (CSF, por sus siglas en inglés: *Corsi Span Forward*; CSB, por sus siglas en inglés: *Corsi Span Backward*). El producto de ambas puntuaciones da como resultado la puntuación total (TSF, por sus siglas en inglés: *Total Score Forward*; TSB, por sus siglas en inglés: *Total Score Backward*), que ha demostrado ser la variable más fiable para evaluar los cambios en este test de memoria visoespacial (Kessels et al., 2000).

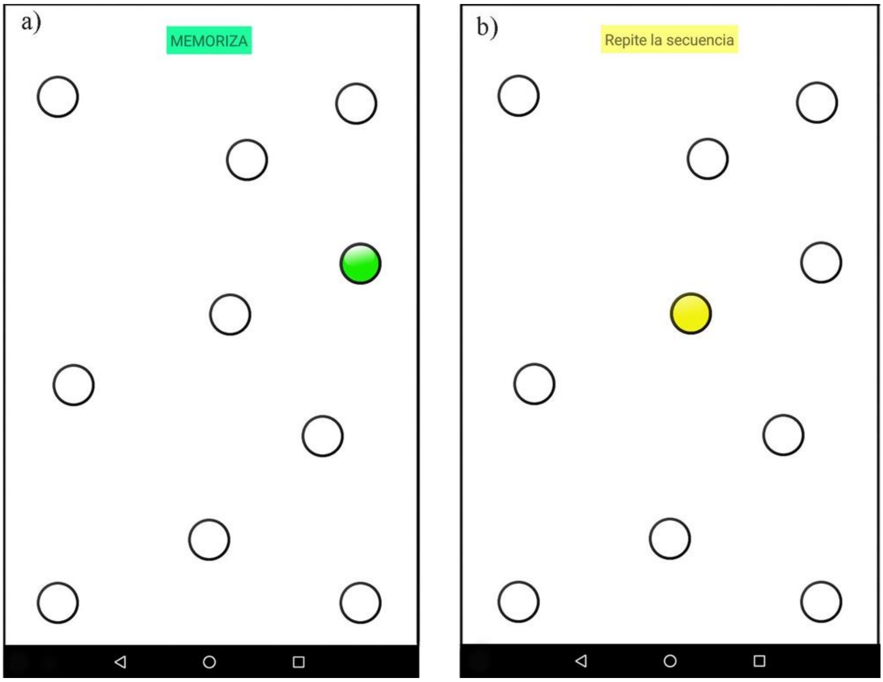

Figura 5. Test de Corsi. **a**) Condición *Forward*; **b**) Condición *Backward*.

3.4.3.2.2. Memoria declarativa

La memoria declarativa se evaluó a través una tarea de memoria formal basada en el estudio previo de Izquierdo et al. (2008), donde los sujetos debían memorizar un texto de 15 líneas (221 palabras) con información objetiva. A los participantes se les dio 10 min antes de cada situación experimental (sesiones de MICT y de HIIT), situándose estas después de la codificación de memoria, durante la primera fase de la consolidación de la memoria (Roig et al., 2016). El recuerdo de la memoria, a su vez, se pidió después (Loprinzi, Roig, et al., 2021) de 48 h y siete días utilizando una lista de preguntas sobre diez elementos fácticos de cualquiera de los dos textos (Izquierdo et al., 2008). Por cada respuesta correcta, los participantes recibieron un punto.

3.4.3.3. Lactato Sanguíneo

Para determinar las concentraciones de lactato se obtuvieron muestras de sangre del lóbulo de la oreja de los sujetos utilizando un analizador de lactato portátil (Lactate Scout, SensLab GmbH, Leipzig - Alemania).

3.4.3.4. Análisis genético

Las muestras de saliva, utilizadas para conocer el SNP de BDNF, se obtuvieron con un kit de recolección de saliva de ADN OrageneTM (DNA Genotek SL, Ottawa, ON, Canadá). El protocolo de extracción de ADN fue proporcionado por el fabricante. La muestra se analizó posteriormente mediante una PCR cuantitativa StepOne plus de Applied Biosystem (Thermo Fisher Scientific SA, Waltham, MA, EE. UU.), siguiendo el protocolo de Sánchez-Romero et al. (2009).

3.5. Análisis Estadístico

A nivel estadístico Alfa se fijó en 0.05 para todos los análisis incluidos en los estudios. En todos los estudios se realizaron pruebas de ANOVA de medidas repetidas para la evaluación de los cambios en las diferentes variables dependientes incluidas en los estudios: Velocidad de procesamiento (*estudio crónico*); Estado afectivo y Vitalidad subjetiva (Bienestar psicológico) (*estudios crónico y agudo 1*); Velocidad de procesamiento y control inhibitorio (*estudio agudo 1*); Memoria visoespacial y declarativa (*estudio agudo 2*).

En el caso del *estudio crónico* existió un factor intersujeto (Tratamiento), al dividir la muestra en grupo experimental y grupo control, y un factor intra sujeto (Tiempo). En los estudios agudo 1 y 2 se utilizó el mismo diseño de medidas repetidas donde todos los participantes realizaron todas las condiciones de estudio, siendo todos los factores incluidos intrasujeto (Tiempo y Tratamiento).

La esfericidad de las pruebas se evaluó con la prueba de esfericidad de Mauchly en cada uno de los estudios. Si no se cumplió el supuesto de esfericidad, se aplicaron las correcciones de Greenhouse-Geisser. Para las comparaciones múltiples en los análisis post hoc se realizaron pruebas t con ajustes de Bonferroni cuando se identificaron resultados significativos en el análisis ANOVA. Como medida de los tamaños del efecto en el análisis ANOVA RM, se utilizó eta-cuadrado parcial (η_p^2) y se agrupan como pequeño ($\leq$ 0.01), mediano ($\leq$ 0.06) y grande ($\leq$ 0.14) (Cohen, 1992).

También se utilizaron pruebas t para muestras relacionadas o prueba de los rangos con signo de Wilcoxon para calcular diferencias en algunas variables en los *estudios agudos 1 y 2*, como en los parámetros de intensidad del ejercicio incluidos (FC y Lactato sanguíneo). En el *estudio agudo* 2 también se utilizó este tipo de prueba para comparar la memoria declarativa (cantidad de recuerdos) entre las dos intensidades de ejercicio incluidas en el protocolo.

Como medida del tamaño del efecto de las diferentes pruebas t utilizadas en los estudios, se utilizó la *d* de Cohen, expresándoselos resultados obtenidos como pequeños ($\leq$ 0.20), medianos ($\leq$ 0.50) y grandes ($\leq$ 0.80) (Cohen, 1992).

Adicionalmente a los análisis principales comentados, en los *estudios agudos* se realizaron ANOVA RM por separado para el polimorfismo de BDNF (Val/Val, Val/Met o Met/Met) o el sexo como factor entre sujetos para analizar las posibles influencias de estos factores no modificables.

Por último, también se realizaron los análisis de correlación de Pearson (*r*). Por un lado, en los *estudios agudos* para establecer posibles asociaciones entre los incrementos (Δ) (Valor posterior – Valor previo) en el lactato sanguíneo y las funciones cognitivas analizadas en cada uno de ellos y el bienestar psicológico en el caso del *estudio agudo 1*. Por otro lado, en el *estudio crónico* se utilizó para analizar las relaciones entre las diferentes variables de bienestar psicológico utilizadas.

Para todos los análisis incluidos en la presente tesis se utilizó el software estadístico JASP 0.16 (Eric-Jan Wagenmakers, Departamento de Métodos Psicológicos de la Universidad de Ámsterdam, Nieuwe Achtergracht 129B, Ámsterdam, Países Bajos).

CAPÍTULO 4

RESUMEN DE LOS RESULTADOS

Capítulo 4. Resumen de los resultados

4.1. Efecto crónico del ejercicio en la función cognitiva y el bienestar psicológico

Respecto a las medidas principales, el análisis de ANOVA reveló un efecto de interacción Tiempo (PRE-POST5-POST10) x Tratamiento (HIFT-Control), tanto en el CRT ($F_{(1,40)} = 3.60$, $p = 0.03$, $\eta_p^2 = 0.09$) como en el InT ($F_{(1,40)} = 5.66$, $p < 0.01$, $\eta_p^2 = 0.12$). Las pruebas post-hoc de Bonferroni indicaron mejoras en los tiempos de reacción solo en el grupo experimental tanto en el CRT (POST5: Δ = -46.77 ms, $t_{(19)} = 3.23$, $p = 0.02$, $d = 0.72$; POST10: Δ = -59.93 ms, $t_{(19)} = 4.14$, $p < 0.01$, $d = 0.93$) como en el InT (POST10: Δ = -73.61 ms, $t_{(19)} = 3.20$, $p = 0.03$, $d = 0.70$), sugiriendo una mejora crónica con el programa de HIFT en la velocidad de procesamiento.

Todas las variables determinantes del bienestar psicológico incluidas (estado afectivo positivo, estado afectivo negativo y vitalidad subjetiva) desde las dos perspectivas (hedónica y eudaimónica) correlacionaron entre sí significativamente ($p < 0.05$) en todos los momentos de medición (PRE, POST5 y POST10). Respecto a los resultados principales, el análisis ANOVA no reveló diferencias entre los grupos para ninguna de las variables ($p > 0.05$), por lo que ni la fase de entrenamiento presencial ni durante la fase de confinamiento afectaron al bienestar psicológico.

También observamos como la intensidad del programa presencial se mantuvo durante las sesiones del periodo de cuarentena ($p > 0.05$), pero sí que existió una reducción significativa ($p < 0.05$)

en la adherencia al programa durante la cuarentena respecto al programa presencial (94% vs 71%).

Por último, se incluyó el sexo en los análisis como posible factor influyente en la respuesta cognitiva o en el bienestar. Sin embargo, la prueba de ANOVA no reflejó diferencias por sexo en la respuesta de ninguna de las variables cognitivas ni de bienestar psicológico ($p > 0.05$).

4.2. Efecto agudo del ejercicio en la función cognitiva y el bienestar psicológico.

4.2.1. Velocidad de procesamiento y control inhibitorio

Tras los análisis de la prueba ANOVA, observamos un efecto significativo en la interacción Tiempo (PRE-POST) x Tratamiento (HIIT-MICT-Control) para los tiempos de reacción en todas las condiciones del test Stroop: Congruente: ($F_{(2, 70)} = 20.14$, $p < 0.001$, $\eta_p^2 = 0.37$); Fase Neutral: ($F_{(2, 70)} = 4.99$, $p < 0.01$, $\eta_p^2 = 0.13$); Fase Incongruente: ($F_{(2, 68)} = 8.07$, $p < 0.001$, $\eta_p^2 = 0.19$).

Analizando las pruebas post hoc para la condición congruente (velocidad de procesamiento), tanto el HIIT (Δ = -64.24 ms, $t_{(35)}$ = 9.46, $p < 0.001$, $d = 1.58$) como el MICT (Δ = -27.86 ms, $t_{(35)} = 4.10$, $p = 0.001$, $d = 0.68$) produjeron reducciones en el tiempo de reacción, siendo superior el tamaño del efecto del HIIT. Sin embargo, para la condición neutral, únicamente el HIIT provocó mejoras en el tiempo de reacción (Δ = -45.02 ms, $t_{(35)} = 5.01$, $p < 0.001$, $d = 0.84$). Cuando observamos los análisis poshoc en la condición incongruente (control inhibitorio), únicamente el HIIT provocó cambios significativos (Δ =

-81.62 ms, $t_{(34)} = 5.53$, $p < 0.001$, $d = 0.93$). No se observaron cambios significativos para ninguna de las variables tras la situación control ($p > 0.05$), ni diferencias entre los valores pre entre las situaciones experimentales ($p > 0.05$).

Estas mejoras en el tiempo de reacción provocadas por el ejercicio, sumadas a la ausencia de diferencias en los índices de precisión entre los tratamientos para todas las condiciones del test Stroop ($p > 0.05$), indican que los cambios positivos del ejercicio (tanto en velocidad de procesamiento como en control inhibitorio) se debieron a respuestas más rápidas y no como resultado de una respuesta compensatoria entre velocidad y precisión.

4.2.2. Memoria

Respecto a la memoria visoespacial (condiciones *forward y backward*), la prueba de ANOVA de medidas repetidas no mostró un efecto de interacción Tiempo (PRE-POST) x Tratamiento (MICT-HIIT) para *forward* (CSF y TSF) ($p > 0.05$), aunque si que apareció dicho efecto para la condición *backward*, tanto para el CSB ($F_{(1,34)} = 6.67$, $p = 0.01$, $\eta_p^2 = 0.16$) como para el TSB ($F_{(1,34)} = 6.79$, $p = 0.01$, $\eta_p^2 = 0.17$). El análisis post hoc mostró mejoras pre-post solo en el TSB tras el HIIT ($t_{(34)} = 2.87$, $p = 0.03$, $d = 0.5$).

Respecto a la memoria declarativa, se encontraron diferencias en el recuerdo de información factual a las 48 h a favor de la sesión de HIIT ($p = 0.04$, $d = 0.34$), pero no a los 7 días ($p > 0.05$).

4.2.3. Bienestar psicológico

Observamos un efecto significativo para la prueba de ANOVA en la interacción Tiempo (PRE-POST) x Tratamiento (HIIT-MICT-Control) para la vitalidad subjetiva ($F_{(1.57, 53.53)} = 4.70$, $p = 0.02$, $\eta_p^2 = 0.12$) y para el estado afectivo positivo ($F_{(1.57, 53.35)} = 4.65$, $p = 0.02$, $\eta_p^2 = 0.12$). En este sentido, ambos protocolos de ejercicio (HIIT y MICT) tendieron a mejorar la vitalidad subjetiva, mientras que únicamente el MICT tendió a mejorar el estado afectivo positivo. No se observó ningún efecto significativo de interacción para el estado afectivo negativo ($p > 0.05$).

4.3. Posibles mecanismos o mediadores de los efectos agudos del ejercicio en la función cognitiva:

4.3.1. Lactato

Respecto a la velocidad de procesamiento y el control inhibitorio, se identificaron correlaciones significativas entre la liberación de lactato y los cambios en los tiempos de reacción en condición congruente ($r = -0.49$, $p < 0.001$) y condición incongruente ($r = -0.28$, $p < 0.01$). Cuando se analizó cada situación experimental por separado (HIIT, MICT y Control) únicamente el HIIT mostró correlaciones significativas entre lactato liberado y cambios en tiempo de reacción en la condición congruente del test Stroop (velocidad de procesamiento). Esta observación no se cumplió para ninguna otra combinación entre condición Stroop y protocolo experimental ($p > 0.05$ en todos ellos).

En relación a las variables de memoria, identificamos correlaciones positivas entre la liberación de lactato y las puntuaciones de memoria alcanzadas para la condición *backward* de memoria visoespacial (CSB: $r = 0.32$, $p < 0.01$; TSB: $r = 0.43$, $p < 0.001$) y para el recuerdo de información de memoria declarativa a las 48 horas ($r = 0.26$, $p = 0.02$). Cuando se analizó cada situación experimental por separado (HIIT y MICT) únicamente se observaron correlaciones significativas en la memoria visoespacial (TSB, concretamente) en el HIIT ($r = 0.50$, $p < 0.01$). Esta observación no ocurrió en el MICT para ninguna variable de memoria ($p > 0.05$).

4.3.2. Polimorfismo genético de BDNF

No se observó un efecto principal de la codificación genética de BDNF (Val/Val, Val/Met o Met/Met) para ninguna variable cognitiva ($p > 0.05$) ni en las interacciones con el Tiempo y Tratamiento (p > 0.05), indicando que el genotipo no moduló los resultados principales (el HIIT es superior para optimizar las ganancias cognitivas, independientemente del polimorfismo genético de BDNF), ni tampoco la función cognitiva de forma aislada del ejercicio.

4.3.3. Sexo de los participantes

El sexo no mostró un efecto principal para ninguna de las variables de memoria analizadas, ni moduló la interacción Tiempo x Tratamiento ($p > 0.05$), indicando que el genotipo no moduló los resultados principales (el HIIT es superior para optimizar las ganancias cognitivas, independientemente del sexo).

4.3.3. Bienestar psicológico

Observamos una correlación entre los cambios en el bienestar psicológico (concretamente la vitalidad subjetiva) y los tiempos de reacción en la condición congruente del test de Stroop ($r = -0.22$, $p = 0.02$), lo que indica que a mayor cambio en la vitalidad subjetiva más rápida es la respuesta cognitiva.

CAPÍTULO 5

RESUMEN DE LA DISCUSIÓN

Capítulo 5. Resumen de la discusión

Los estudios incluidos en la presente tesis trataron de analizar los efectos agudos y crónicos del ejercicio físico en la función cognitiva y el bienestar psicológico de jóvenes estudiantes universitarios. Para ello, se adoptó una perspectiva dosis-respuesta, teniendo en cuenta otros moderadores tratando de optimizar la respuesta, así como diferentes mecanismos neurobiológicos y psicosociales/conductuales que pueden estar actuando de manera subyacente en los cambios

Los principales hallazgos fueron que el ejercicio de alta intensidad logró resultados positivos en la función cognitiva, tanto a nivel agudo como crónico. En cuanto al bienestar psicológico, parece existir un impacto positivo del ejercicio a nivel agudo, tanto con el HIIT como con el MICT en algunas de las variables que lo componen, algo que no pudimos corroborar a nivel crónico. Por otro lado, en busca de posibles mediadores o mecanismos subyacentes por los cuales el ejercicio pueda mejorar la cognición observamos, desde un punto de vista neurobiológico, relaciones entre los cambios cognitivos a nivel agudo con los incrementos de lactato sanguíneo tras el ejercicio. Desde un punto de vista psicosocial/conductual, algunos componentes del propio bienestar psicológico también parecen relacionados con los cambios agudos cognitivos. Sin embargo, el polimorfismo genético de BDNF, otra variable que ha sido ampliamente utilizada en la literatura como posible mediador neurobiológico de los efectos, no influyó en los resultados cognitivos ni a nivel basal, ni en respuesta al ejercicio, así como tampoco lo hizo el sexo.

5.1 Efectos crónicos

A nivel crónico, observamos como un programa de ejercicio de alta intensidad (HIFT) provocó mejoras en la velocidad de procesamiento a las 5 y a las 10 semanas, pero no impactó en el bienestar psicológico. Además, la fase de confinamiento por COVID-19 (semanas 6-10 del programa) no pareció tener un impacto en la salud mental, al no afectar a ninguna de las variables analizadas (función cognitiva y bienestar psicológico) respecto a la fase de entrenamiento presencial (primeras 5 semanas), siguiendo un comportamiento similar en ambas fases. Sin embargo, aunque los entrenamientos durante la fase de confinamiento no difirieron en intensidad respecto a la fase presencial, mostrando la posibilidad de adaptar este tipo de programas en dichas situaciones tan excepcionales, si se observó una reducción en la adherencia al programa respecto a la primera fase.

5.1.1. Función cognitiva

Estos resultados a largo plazo son acordes a los obtenidos en otros trabajos previos donde se ha visto como la actividad física de moderada a vigorosa intensidad produce mejoras a nivel crónico en el rendimiento académico y diferentes funciones cognitivas como la velocidad de procesamiento, la memoria y la FE en diferentes fases de la vida (Erickson et al., 2019). Además, específicamente hablando de ejercicio físico crónico y población joven, algunos estudios han observado beneficios cognitivos en velocidad de procesamiento y otras variables cognitivas relacionadas con la memoria y la FE tras programas de ejercicio (Haverkamp et al., 2020; Loprinzi et al., 2018; Stern et al., 2019). Sin embargo, es alta la heterogeneidad existente en la magnitud de estos efectos (Herold et al., 2019), existiendo diferentes moderadores, como la frecuencia, la intensidad, el volumen, el tipo o el contexto del ejercicio que pueden estar contribuyendo a un mayor o menor impacto (Lubans et al., 2022; Lubans et al., 2016), por lo que deberían ser controladas para intentar reducir la heterogeneidad y seguir avanzando en el conocimiento sobre los protocolos óptimos para producir la ganancias cognitivas con el ejercicio.

5.1.2. Bienestar psicológico

En cuanto al bienestar psicológico, en primer lugar y en línea con lo que se ha visto en estudios previos (Cervelló et al., 2014), encontramos que tanto los componentes hedónicos como eudaimonicos del bienestar están estrechamente relacionados entre sí (estado afectivo y vitalidad subjetiva). Sin embargo, en contra de nuestra hipótesis, ni la fase de entrenamiento presencial ni la fase de entrenamiento en cuarentena afectaron a esta variable. Estos datos contradicen a una gran cantidad de estudios previos que han observado que el ejercicio es una herramienta efectiva para mejorar el bienestar psicológico de jóvenes estudiantes (Cervelló et al., 2014; Eather et al., 2019; Garcia et al., 2015; Mandolesi et al., 2018). Además, esperábamos que el periodo de cuarentena impactara negativamente en la salud mental de los participantes (Brooks et al., 2020; Burke et al., 2020), implicando reducciones en la adherencia al ejercicio, el bienestar psicológico y reducción en las ganancias de función cognitiva respecto a la fase presencial. Si que observamos reducciones en la adherencia al programa durante el periodo de cuarentena, que podría venir explicada desde la teoría de la autodeterminación (Ryan & Deci, 2000), por una falta de satisfacción de las 3 necesidades psicológicas básicas (autonomía, competencia y relación) durante esta fase, como por ejemplo la ausencia de la dimensión relación, que se ha visto previamente como puede influir en la adherencia al ejercicio (Kang, Lee, & Kwon, 2020). Incluso aspectos como la propia supervisión de profesionales cualificados, característica fundamental de los programas de entrenamiento presenciales, podría estar actuando en ello también (Garber et al., 2011). Sin embargo, aunque si se observaron reducciones de la adherencia al programa, las variables relacionadas con la salud mental (bienestar psicológico y cognición) no se vieron afectadas negativamente en esta fase (siguiendo una progresión similar a la de la primera fase del programa), sugiriendo que la población joven, al no tener la misma carga de responsabilidades que la población adulta, experimentarían menos impacto en estas variables durante una situación extraordinaria como un confinamiento domiciliario (Brooks et al., 2020).

Las mejoras cognitivas observadas podrían venir explicadas por cambios producidos en la condición física tras el programa de entrenamiento, puesto que previamente se han observado relaciones entre ambas variables (Aberg et al., 2009; Luque-Casado et al., 2013; Wang et al., 2015). No obstante, como consecuencia del periodo de confinamiento por COVID-19, y sus restricciones sociales, no pudimos valorar las mejoras esperadas por el programa en la condición física. Sin embargo, más allá de la propia condición física y desde una perspectiva más profunda, tal y como indican trabajos previos (Lubans et al., 2016; Stillman et al., 2016), los cambios cognitivos con el ejercicio podrían venir explicados por diferentes mecanismos (neurobiológicos y psicosociales/conductuales). Tradicionalmente, la literatura se ha centrado en los mecanismos neurobiológicos, y falta evidencia para comprender las relaciones entre los cambios psicosociales y conductuales con el funcionamiento cognitivo (Stillman et al., 2016). Desde este enfoque, esperábamos que el bienestar psicológico mejoraría de forma paralela con la función cognitiva, siguiendo una evolución similar, dada la influencia mutua que tienen ambas variables (Mandolesi et al., 2018). Sin embargo, el programa de ejercicio, a pesar de provocar mejoras en la función cognitiva, no modificó el bienestar psicológico de los sujetos siguiendo una evolución independiente ambas variables. De esta forma, probablemente los cambios crónicos en la función cognitiva podrían haber sido mediados por mecanismos neurobiológicos o por otros mecanismos de tipo psicosocial no analizados (Lubans et al., 2016; Stillman et al., 2016).

Como consecuencia de estos resultados obtenidos en el *estudio crónico*, y de la necesidad de conocer que aspectos subyacen a las mejoras cognitivas con el ejercicio, se plantearon los dos siguientes estudios de la tesis, teniendo en cuenta diferentes moderadores y potenciales mecanismos subyacentes (Lubans et al., 2022; Lubans et al., 2016; Stillman et al., 2016).

5.2. Efectos agudos

5.2.1. Función cognitiva

A raíz de los estudios agudos, observamos como el HIIT fue un protocolo de ejercicio óptimo para potenciar la función cognitiva. Aunque MICT también tuvo efectos positivos significativos en la velocidad de procesamiento, la magnitud del efecto fue mayor para el HIIT, mientras que en el resto de variables cognitivas, control inhibitorio y memoria, únicamente el HIIT produjo efectos significativos.

Estos resultados son acordes a los observados en un reciente metaanálisis, donde las intensidades de ejercicio más altas conseguirían los mayores efectos en la cognición (HIIT > ejercicio continuo vigoroso > MICT) (Oberste et al., 2019). Otros estudios previos en personas jóvenes han observado resultados similares, donde el HIIT puede ser un protocolo óptimo para mejorar la atención selectiva y el control inhibitorio (Herold et al., 2022; Li et al., 2022; Tsukamoto et al., 2016) o la memoria (Li et al., 2022; Martínez-Díaz, Escobar-Muñoz, & Carrasco, 2020; Wilke, 2020). No obstante, otras investigaciones han observado una relación de U invertida entre la intensidad del ejercicio y la cognición, con mejores respuestas en intensidades moderadas respecto a las más ligeras o altas (Pontifex et al., 2019). En esta línea, algunos estudios realizados en muestras similares a la de la presente tesis, indican como entre dos protocolos de ejercicio continuo (de intensidad moderada y vigorosa), únicamente el ejercicio de intensidad moderada condujo a una mejora aguda de la FE respecto a la situación control (Loprinzi & Kane, 2015). Sin embargo, en un trabajo más reciente, los mismos autores observaron mejoras en la memoria después de una sesión de alta intensidad, una vez más en jóvenes estudiantes universitarios (Loprinzi, Day, et al., 2021). Además, un metaanálisis reciente encontró que los efectos agudos del ejercicio de alta intensidad (importante remarcar que incluían cualquier ejercicio de alta intensidad, no limitado a los protocolos de HIIT como los utilizados en la presente tesis) solo diferían de la situación control sin ejercicio, pero no de los protocolos de ejercicio moderado (Moreau & Chou, 2019). En este sentido, podría ser necesario diferenciar al HIIT de otros protocolos de alta intensidad puesto que el HIIT puede provocar grandes cantidades de lactato, que puede actuar de manera subyacente en los efectos positivos en la cognición, pero un limitado estrés mental que impactaría negativamente en la función cognitiva tras otros protocolos de alta intensidad (Hashimoto et al., 2018), por lo que podría ser conveniente analizar sus efectos de forma separada respecto a otros protocolos de entrenamiento considerados de alta intensidad.

5.2.2. Bienestar psicológico

En relación al bienestar psicológico, aunque en el *estudio crónico* no observamos una influencia del programa de ejercicio en el bienestar, en el *estudio agudo 1* si observamos posibles efectos positivos con el ejercicio. Existe evidencia consistente de que el ejercicio físico presenta muchos beneficios en personas de cualquier edad en la mejora del bienestar psicológico (Mandolesi et al., 2018). En este sentido, se observó un impacto positivo después de ambos protocolos de ejercicio (HIIT y MICT) para la vitalidad subjetiva. En términos de estado afectivo positivo, únicamente el MICT produjo mejoras. Para el estado afectivo negativo, no hubo ningún efecto de interacción entre las diferentes situaciones de estudio. A diferencia de los resultados mostrados por Cervelló et al. (2014), en nuestro estudio, el ejercicio físico mejoró la vitalidad subjetiva del bienestar psicológico independientemente de la intensidad del mismo. Sin embargo, únicamente el MICT mejoró el estado afectivo positivo, en contra de los mejores resultados vistos por Cervelló et al. (2014) con la alta intensidad. Esto sugiere que, en general, el bienestar psicológico puede ser mejorado con el ejercicio físico, al menos de forma aguda, independientemente de la intensidad del mismo para algunos de sus componentes, mientras que para otros existe controversia respecto a qué intensidad sería más beneficioso.

5.3. Influencia de los moderadores

Ya se ha ido comentando la heterogeneidad que existe en la literatura sobre ejercicio y cognición a lo largo del texto. Por ello, se hace importante analizar los resultados de los estudios teniendo en cuenta algunos factores que pueden estar actuando como moderadores de dicha relación (Lubans et al., 2022; Lubans et al., 2016) y que pueden optimizar futuros protocolos de ejercicio que persiguen mejoras cognitivas.

En este sentido, la dosis de ejercicio podría ser un elemento clave para maximizar las ganancias. En nuestro caso, fijamos el volumen de las sesiones dentro del rango establecido como óptimo previamente (20 min) (Y. K. Chang et al., 2019; Li et al., 2022;

Oberste et al., 2019), para analizar el efecto aislado de la intensidad del ejercicio, obteniendo, bajo estas circunstancias, las mejores respuestas con la alta intensidad del HIIT, como se ha comentado. Otro aspecto que puede interactuar con la dosis de ejercicio y que se ha estudiado en la literatura es la latencia tras la finalización del ejercicio para producir los efectos. En este sentido, parece que al dejar un tiempo tras las sesión aguda, se promoverían los efectos positivos del ejercicio de alta intensidad (Y. K. Chang et al., 2012), algo que corroboramos con nuestros resultados. Tener en cuenta este elemento podría ser clave, ya que la falta de efectos positivos, del ejercicio de alta intensidad, observada en algunos estudios previos, podría deberse a la administración de las pruebas cognitivas durante o poco después del estímulo, lo que puede enmascarar los beneficios de este tipo de ejercicio debido a la fatiga o excitación desproporcionada producida (Roig et al., 2016).

Por otro lado, cuando hablamos específicamente de memoria, un aspecto que puede influir en la respuesta es la ubicación del estímulo de ejercicio en relación a las diferentes fases de la memoria. De este modo, decidimos abordar la fase de consolidación, situando la sesión de ejercicio después de la etapa de codificación para la memoria verbal (Roig et al., 2016), observando diferencias en el recuerdo de información a las 48 horas entre el HIIT y el MICT, con una correlación positiva entre la cantidad de información recordada y el lactato liberado con el ejercicio. Esto podría estar relacionado con la alteración de diferentes neuroquímicos que aumentan su disponibilidad para los tejidos durante esta fase (Loprinzi, Roig, et al., 2021; Roig et al., 2016). Así, la posible producción de algunas neurotrofinas como el BDNF y su posible vinculación con el lactato liberado tras el HIIT, podrían estar explicando estos resultados (Roig et al., 2016). Por ello, debido a este aumento de disponibilidad de BDNF y otros neuroquímicos durante las fases de codificación y/o consolidación de la memoria, puede ser relevante ubicar el estímulo de ejercicio temporalmente cerca del proceso de aprendizaje.

Por último, debemos hablar sobre los efectos de un factor no modificable como el sexo, el cual no moduló los resultados cognitivos tras el ejercicio ni a nivel agudo ni a nivel crónico en nuestros estudios. Estudios previos han observado que la liberación de BDNF tanto después del ejercicio agudo (Szuhany et al., 2015), como después de un periodo de entrenamiento (Szuhany et al., 2015) podría ser mayor en hombres que en mujeres, lo que podría traducirse en mayores mejoras en la función cognitiva. Sin embargo, Barha et al. (2017), encontraron que las mejoras cognitivas eran más pronunciadas en mujeres, aunque otros estudios han indicado que este efecto de moderación es pequeño (Falck et al., 2019). Así, también existen estudios que muestran ganancias cognitivas más atenuadas en mujeres que en hombres (Ludyga et al., 2020). Esta inconsistencia podría explicarse por diferencias metodológicas entre los estudios, como variaciones en la prescripción de la dosis de ejercicio (Ludyga et al., 2020), o como ya se ha comentado a lo largo de la tesis, a la selección preferencial de adultos mayores en los estudios sobre cognición y ejercicio (Ludyga et al., 2020). Por ello, aunque en personas mayores sí que parece existir una mejor respuesta en mujeres, debe seguir analizándose estos resultados en otros grupos de población.

En definitiva, se debe tener en cuenta que elementos como la dosis de ejercicio (volumen e intensidad), la latencia para administrar el test cognitivo cuando hablamos de respuesta aguda, la ubicación del estímulo de ejercicio respecto a las distintas fases de la memoria y el aprendizaje o el propio sexo pueden ser algunos de los numerosos aspectos que modulen la respuesta cognitiva al ejercicio agudo y crónico y que, por tanto, deben seguir teniéndose en cuenta para optimizar las intervenciones con tal propósito.

5.4. Mecanismos explicativos de los cambios cognitivos

En relación a los mecanismos subyacentes propuestos, observamos la posible relación con los efectos cognitivos producidos de algunos de ellos como el lactato liberado y dimensiones del bienestar psicológico, mientras que no existió influencia alguna del polimorfismo genético de BDNF en ninguno de los estudios donde se analizó.

5.4.1. Lactato sanguíneo

Atendiendo a los posibles mecanismos desde el nivel neurobiológico, observamos relaciones entre el lactato liberado y los cambios cognitivos producidos. Esto ocurrió tanto en la velocidad de procesamiento y el control inhibitorio (*estudio agudo 1*), como en las variables analizadas relacionadas con la memoria (*estudio agudo 2*). Curiosamente, la relación más fuerte (*estudio agudo 1*) ocurrió entre el HIIT y la velocidad de procesamiento, variable que se vio afectada positivamente a nivel crónico por el programa de HIFT en el *estudio crónico*, cuando hipotetizamos que el lactato podría haber sido uno de los mecanismos explicativos de las mejoras. Estos resultados estarían en consonancia con otros estudios de carácter agudo que han observado dichas relaciones entre el lactato sistémico producido con el ejercicio agudo y la función cognitiva (Hashimoto et al., 2018; Herold et al., 2022; Kujach et al., 2019; Skriver et al., 2014).

En este sentido, cuando hablamos de los efectos agudos directos del lactato, se ha comprobado que la captación de lactato por el cerebro está determinada por la concentración de lactato arterial y que cuando el suministro se reduce se podría reducir la función cognitiva potenciada previamente por el HIIT (Hashimoto et al., 2018). Tal y como se ha comentado previamente, dicho lactato, proveniente del musculo esquelético durante el ejercicio, podría aumentar la actividad neuronal y regular el funcionamiento del sistema cerebrovascular, así como los estados redox, todo ello en respuesta al ejercicio, lo que indicaría la importancia del ejercicio físico intenso en la función cerebral (Hashimoto et al., 2021).

Además de estos efectos directos, el lactato también podría estar actuando en el SNC de forma indirecta, efectos que estarían relacionados principalmente con su correlación con la concentración de BDNF a nivel sanguíneo (Ferris et al., 2007; Gibbons et al., 2023; Müller et al., 2020). De este modo, estudios previos en ratones han observado como el lactato liberado por el ejercicio puede cruzar la barrera hematoencefálica induciendo la expresión de BDNF en el hipocampo y mejorando la memoria (El Hayek et al., 2019). Esto podría explicar los resultados obtenidos en el *estudio crónico* a través del programa de HIFT. La alta liberación de lactato producida por este tipo de programas (Ferguson et al., 2018) supondría una exposición continua al lactato, lo que a su vez induciría la liberación de BDNF para producir los efectos crónicos (Hashimoto et al., 2021). A favor de esta hipótesis, un estudio previo mostró como un programa de HIFT de 3 meses aumentó significativamente los niveles de BDNF en reposo en adultos jóvenes (Murawska-Cialowicz, Wojna, & Zuwala-Jagiello, 2015). Por lo tanto, esto sugiere que los efectos crónicos en la cognición podrían ser consecuencia de la actuación indirecta del lactato, desencadenando la liberación de BDNF y, finalmente, produciendo las mejoras cognitivas.

Con los hallazgos obtenidos en nuestros estudios, apoyados en la evidencia existente que muestra los posibles efectos directos e indirectos del lactato en el SNC y, por ende, en la cognición, sugerimos el posible papel subyacente del lactato en las mejoras cognitivas, agudas y crónicas, producidas con el ejercicio.

5.4.2. Polimorfismo genético de BDNF

Pese a que algunos estudios han observado que los sujetos con la presencia del alelo Met pueden tener efectos cognitivos reducidos en la respuesta al ejercicio respecto a aquellos con la codificación Val/Val (Canivet et al., 2015; Hopkins et al., 2012), en nuestros estudios no encontramos un efecto moderador de Val66Met en ninguna de las variables cognitivas analizadas ni a nivel basal, ni en respuesta al ejercicio. Sin embargo, se ha sugerido que gran parte de los estudios que han observado efectos moderadores del polimorfismo de BDNF Val66Met en la relación ejercicio-cognición han sido de tipo transversal, los cuales en su gran mayoría fueron llevados a cabo en adultos mayores (de Las Heras et al., 2022). Por ello, en la literatura previa, se ha destacado la necesidad de estudiar el posible efecto moderador del polimorfismo genético de BDNF en la relación entre ejercicio y cognición en personas jóvenes (Kujach et al., 2019; Lubans et al., 2022).

De acuerdo con los resultados obtenidos, algunos autores han sugerido que los efectos genéticos de Val66Met sobre el rendimiento cognitivo podrían estar ocurriendo en etapas más avanzadas de la vida, durante el envejecimiento (Lindenberger et al., 2008), lo cual podría explicar la ausencia efecto moderador del polimorfismo en nuestra muestra de jóvenes estudiantes. Además, revisiones recientes de la literatura sobre este tópico que han incluido tanto estudios en jóvenes como en mayores, aunque sugieren que ciertas formas de memoria pueden mejorar con el ejercicio en mayor medida en sujetos con la codificación Val/Val que en portadores Met (Liu, Li, Colton, Ge, & Li, 2020), indican que, en general, la evidencia es inconsistente en cuanto a efectos significativos sobre la cognición e incluso a la dirección de estos efectos (de Las Heras et al., 2022; Liu et al., 2020). Por otro lado, además de la edad como posible moderador, otros aspectos como las diferencias metodológicas, el sexo, las interacciones con otros genes o la etnia pueden estar influyendo en los resultados dispares obtenidos (de Las Heras et al., 2022). En definitiva, nuestros resultados, y de acuerdo con la literatura más reciente (de Las Heras et al., 2022), sugieren que los beneficios del ejercicio sobre la cognición podrían ser independientes del perfil genético de BDNF, al menos en personas jóvenes, pudiendo todos los individuos beneficiarse, de una forma equiparable, de los efectos cognitivos del ejercicio. Para apoyar esa hipótesis se requiere de más estudios que incluyan esta variable como posible moderadora de los efectos cognitivos del ejercicio en diferentes etapas de la vida.

5.4.3. Bienestar psicológico

Como último potencial mecanismo, este de tipo psicosocial (Lubans et al., 2016; Stillman et al., 2016), que pudiera mediar en los efectos del ejercicio en la cognición, se ha visto como el bienestar psicológico puede influir en la función cognitiva a través de circuitos cerebrales específicos que involucran áreas prefrontales y estructuras límbicas (Barbas, 2000; Mandolesi et al., 2018). En nuestro caso, a nivel crónico observamos mejoras de la función cognitiva, mientras que el bienestar psicológico permaneció inalterado. Sin embargo, a nivel agudo observamos asociaciones entre los cambios en la velocidad de procesamiento (condición congruente en la tarea de Stroop) y el bienestar psicológico (vitalidad subjetiva), lo que podría sugerir una relación entre las mejoras agudas en el bienestar psicológico y la función cognitiva.

De esta forma, el bienestar psicológico podría estar actuando como un mecanismo de tipo psicosocial, siendo importante para producir algunas de las mejoras cognitivas con el ejercicio agudo (Lubans et al., 2016; Stillman et al., 2016). En esta línea, se ha visto como los beneficios cognitivos agudos del HIIT frente a otros entrenamientos de alta intensidad, que en ocasiones provocan efectos nocivos en la cognición, podrían estar asociados a su propia naturaleza interválica, que conllevaría la liberación de lactato observada, pero limitando el estrés mental producido (Hashimoto et al., 2018). En línea con este hallazgo, y vinculando los mecanismos de tipo neurobiológico y psicosocial, en nuestro caso no observamos diferencias en algunas variables del bienestar psicológico entre las condiciones de ejercicio (HIIT vs MICT), lo que podría sugerir que la alta liberación de lactato sin un impacto negativo paralelo a nivel de bienestar psicológico podría ayudar a conseguir las mejoras cognitivas observadas. Por ello, podría ser que, para favorecer la posible implicación neurobiológica del lactato, u otros metabolitos asociados al ejercicio de alta intensidad, en los beneficios cognitivos, la modalidad de ejercicio utilizada, debería impactar positivamente, o al menos no hacerlo negativamente, aspectos relacionados con el bienestar psicológico que pudieran enmascarar la respuesta positiva en la cognición.

CAPÍTULO 6

CONCLUSIONES DE LA TESIS

Capítulo 6. Conclusiones de la tesis

6.1. Conclusiones generales

Las principales conclusiones que podemos extraer de la presente tesis se resumen en los siguientes puntos:

- Un programa de entrenamiento de alta intensidad (de tipo HIFT) podría tener efectos crónicos positivos en la función cognitiva (velocidad de procesamiento) de jóvenes estudiantes (de acuerdo con *H1*).
- Los componentes hedónicos y eudaimonicos del bienestar se relacionaron estrechamente entre sí (de acuerdo con *H2*).
- El bienestar psicológico, en jóvenes universitarios, no se vio afectado a nivel crónico por el programa de entrenamiento (en desacuerdo con *H3*).
- El periodo de confinamiento domiciliario por COVID-19 (segunda fase del programa de entrenamiento) no afectó a la progresión de las variables cognitivas o de bienestar respecto a la fase presencial del programa (en desacuerdo con *H4*).
- La adherencia al programa se vio reducida durante la fase de entrenamiento en confinamiento respecto a la fase presencial (de acuerdo con *H5*).
- La intensidad del programa HIFT, factor clave de esta modalidad de entrenamiento, se mantuvo durante las sesiones de la segunda fase del programa, durante el confinamiento domiciliario por COVID-19 (de acuerdo con *H6*).

- A nivel agudo, el ejercicio físico funcionó como una herramienta eficaz para mejorar la velocidad de procesamiento y el control inhibitorio (FE), con los mejores resultados obtenidos tras el HIIT (de acuerdo con la *H7*).
- Respecto a los posibles mecanismos subyacentes propuestos, el lactato liberado a nivel sanguíneo, como posible mecanismo neurobiológico, se asoció con los cambios producidos en la velocidad de procesamiento, sugiriendo un posible papel importante en las mejoras cognitivas con el HIIT (de acuerdo con *H8*).
- El polimorfismo genético de BDNF (Val66Met), no modularía los efectos del ejercicio en velocidad de procesamiento y el control inhibitorio, al menos en personas jóvenes (en desacuerdo con *H9*).
- El ejercicio mejoró el bienestar psicológico a nivel agudo. En este sentido, aunque el HIIT podría producir mejoras en algunas dimensiones del bienestar, como la vitalidad subjetiva, de forma similar al MICT, en otras dimensiones como el estado afectivo el MICT podría tener mayores efectos (en desacuerdo con *H10*).
- Como potencial mecanismo subyacente de tipo psicosocial, una de las dimensiones del bienestar psicológico (vitalidad subjetiva) se asoció a las mejoras cognitivas producidas a nivel agudo (específicamente en velocidad de procesamiento), lo que podría sugerir la necesidad de que la modalidad de ejercicio de alta intensidad no provoque estrés

mental o impactos negativos en el bienestar psicológico para promover las ganancias cognitivas (de acuerdo con *H11*).

- El ejercicio provocó una respuesta en la memoria dependiente del lactato liberado, siendo el HIIT superior al MICT y existiendo relaciones entre las mejoras de memoria y dicha liberación de lactato tras el ejercicio (de acuerdo con *H13*).
- La codificación genética individual de BDNF no influyó en los efectos del ejercicio sobre la memoria (en desacuerdo con *H14*).
- El sexo no influyó en los resultados cognitivos tras el ejercicio en jóvenes universitarios (en desacuerdo con la *H15*).

6.2. Limitaciones y direcciones futuras

A nivel crónico, en el estudio 1, como consecuencia de la cuarentena por COVID-19 no pudimos realizar las mediciones de condición física posteriores al programa, por lo que no pudimos comprobar si los cambios observados en el funcionamiento cognitivo están relacionados con mejoras en la condición física, tal y como preveíamos. Además, no realizamos un seguimiento crónico de algunos de los posibles mecanismos que pudieron subyacer las mejoras cognitivas con el programa. Por lo tanto, la discusión sobre los resultados obtenidos se realizó a partir de inferencias basadas en la literatura previa. Futuros estudios de carácter crónico, deberían tener en cuenta alguna de estas variables para comprender mejor lo que subyace a las mejoras cognitivas con el ejercicio crónico.

Respecto a los estudios agudos, en ambos seleccionamos un volumen de ejercicio fijo de 20 min, puesto que parece el volumen óptimo para producir las ganancias cognitivas, y solo modificamos la intensidad. No obstante, podría ser interesante combinar distintos volúmenes e intensidades para conocer la interacción óptima entre las dos variables y tener una idea más amplia de la dosis-respuesta, donde sigue existiendo falta de conocimiento. Por otro lado, inferimos la asociación entre el metabolismo acelerado del lactato cerebral y la mejora de algunas de las funciones cognitivas a partir de los datos sanguíneos de lactato. Sin embargo, no constatamos de forma directa en nuestros estudios el consumo de lactato cerebral para probar nuestras hipótesis y, aunque investigaciones previas lo han corroborado tal y como se ha comentado en reiteradas ocasiones, es un aspecto que debe ser tenido en cuenta como valor añadido en futuras investigaciones. En cuanto a la muestra, dada la complejidad del análisis ANOVA para estudiar el efecto del polimorfismo genético de BDNF (Tiempo x Tratamiento x Polimorfismo BDNF), no conseguimos mantener una potencia de estudio ≥ 0.8, por lo que se requieren muestras más grandes para analizarlo.

Para finalizar, sugerimos que futuras investigaciones deberían centrar su atención en seguir planteando el estudio de la relación ejercicio-cognición desde una perspectiva que incluya algunos de los potenciales mecanismos, desde diferentes niveles. Por ejemplo, a nivel crónico, un aspecto interesante sería conocer si las liberaciones constantes de lactato con un programa de entrenamiento, estarían asociadas a mayor producción de BDNF, y esto provocaría los efectos crónicos de forma dependiente de esa liberación de lactato.

Otro aspecto interesante sería plantear este tipo de investigaciones en un entorno ecológico y con un objetivo práctico directo. En este sentido, podría ser de utilidad conocer como la exposición aguda al ejercicio en el entorno académico, en diferentes momentos clave del proceso de formación de la memoria, teniendo en cuenta las fases de codificación, consolidación y recuperación de la memoria, puede favorecer la retención de información específica, y el aprendizaje, y estar vinculado al rendimiento académico. Llevar estos resultados a un entorno ecológico en personas jóvenes, podría definir realmente si esas mejoras cognitivas agudas tras el ejercicio en la atención o la memoria, podrían traducirse en un mayor aprendizaje o rendimiento académico.

Por otro lado, si la producción de lactato es un potencial aspecto clave para producir las mejoras cognitivas con el ejercicio, es necesario probar otros métodos de entrenamiento que incidan en dicha liberación, como el entrenamiento de fuerza, el entrenamiento en hipoxia o incluso con entrenamiento en restricción parcial del flujo sanguíneo. Esta última modalidad de entrenamiento en restricción del flujo sanguíneo se sabe que puede producir grandes liberaciones de lactato, así como adaptaciones en la fuerza y la hipertrofia, todo ello con la ventaja de hacerlo con cargas e intensidades más bajas, a lo que recientemente se le ha añadido un potencial efecto en la función cognitiva (Yamada et al., 2021). Por todo ello, puede ser determinante para seguir avanzando dentro de los posibles mecanismos explicativos de las mejoras cognitivas con el ejercicio. Además, existen otros muchos potenciales mecanismos de tipo neurobiológico o psicosocial/conductual (Lubans et al., 2016;

Stillman et al., 2016), que pueden estar implicados en los procesos de mejora cognitiva con el ejercicio, que deben ser analizados adicionalmente para seguir aumentando el conocimiento sobre los agentes implicados en la relación entre ejercicio y cognición.

CAPÍTULO 7

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Capítulo 7. Referencias

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CAPÍTULO 8

ANEXOS

ANEXO 1

ESTUDIO CRÓNICO

COVID-19 Quarantine Impact on Well-being and Cognitive Functioning During a 10-Week High-Intensity Functional Training Program in Young University Students.

Nota. Este estudio se encuentra publicado.

Ballester-Ferrer, J. A., Carbonell-Hernández, L., Pastor, D., and Cervelló, E. (2022). COVID-19 quarantine impact on wellbeing and cognitive functioning during a 10-week high-intensity functional training program in young university students. *Front. Behav. Neurosci.* 16:822199. doi: 10.3389/fnbeh.2022.822199

Capítulo 8. Anexos

8.1. Anexo 1

8.1.1. Estudio crónico. COVID-19 Quarantine Impact on Wellbeing and Cognitive Functioning During a 10-Week High-Intensity Functional Training Program in Young University Students

Abstract

Physical exercise can improve cognitive functioning and wellbeing; however, the degree of change in either of these two variables seems to be related to the exercise intensity or type. Therefore, new physical training (PT) programs have been developed to increase exercise efficiency. One such example is high-intensity functional training (HIFT), which has proven to be a time-efficient and highly effective strategy to improve physical fitness. This study analyzed whether HIFT can affect reaction time (RT) and vitality, as well as positive and negative affect. Forty-two college students participated in the study, 21 in the experimental group and 21 in the control group. The experimental group completed 10 weeks of training, five of which were supervised, and the remainder consisted of online training during the COVID-19 quarantine. Participants were evaluated at the beginning, at the end of the 5 weeks of supervised training, and after the 5 weeks of online training. HIFT improved RT without changes in psychological wellbeing during the entire period of training supervised and online. Therefore, during the HIFT program, the quarantine situation did not adversely affect this population's wellbeing, but it did negatively affect adherence to the training program.

Keywords: *reaction-time, exercise, COVID-19, wellbeing, HIFT, quarantine*

INTRODUCTION

It is well-known that acute and chronic physical exercise (PE) affects physical and physiological functions and influences aspects related to cognitive functioning. According to Herold et al. (2019), it is crucial to distinguish between physical activity (PA), acute and chronic PE, and physical training (PT). All muscle activity that increases energy expenditure is PA (Herold et al., 2019). PE is a specific, planned and structured PA. PE may include a single bout (acute PE) or repeated bouts over a short-term or long-term period (chronic PE). Finally, when chronic PE is purposed to increase (or maintain) one or multiple dimensions of fitness, this is known as PT (Herold et al., 2019).

Regarding exercise and cognitive functioning, PA and fitness have been linked to the academic performance of young students (Marques et al., 2018), inhibitory function in young and old subjects (Peruyero et al., 2017; Carbonell-Hernández et al., 2019; Pastor et al., 2019), memory (Erickson et al., 2011; Jeon and Ha, 2017), wellbeing (Cervelló et al., 2014), depression (McMahon et al., 2017), and other cognitive outputs. However, it is not well-known how different variables of the exercise session (e.g., exercise intensity, exercise duration, exercise type) can modulate it. The literature on exercise and cognition has traditionally dealt with non-modifiable parameters like sex or genotype. Less research is available on the modifiable parameters, like the individual dose-response relationship (Herold et al., 2019).

Regarding the dose-response relationship of exercise to improve cognitive functioning and wellbeing, it is clear that exercise intensity does matter. According to wellbeing, low-intensity but not high-intensity aerobic exercise seems more effective in producing acute changes in wellbeing in adolescents (Pastor et al., 2019). However, high-intensity chronic exercise in university students is more efficient in reducing stress and improving wellbeing (Leuchter et al., 2022).

Regarding cognitive functioning, high-intensity aerobic exercise seems to produce greater improvements in other age groups and different cognitive domains like choice reaction time (RT) (Chang et al., 2012). Furthermore, in favor of high-intensity acute exercise, it has been shown that high intensity can produce greater increases in neurotrophins like brain-derived neurotrophic factor (BDNF) (Saucedo Marquez et al., 2015). BDNF promotes neurogenesis, synaptic plasticity, dendritic and axonal growth, and cell survival (Walsh et al., 2020). The BDNF increase with exercise intensity may be related to lactate release (Ferris et al., 2007). It is well-known that high-intensity exercise performance produces a considerable release of lactate (Ferguson et al., 2018), and high-intensity functional training (HIFT) implies high-intensity exercise. Moreover, lactate release is also related to cerebral blood flow and improves neurogenesis, neuroprotection, neuronal plasticity, and memory (Hashimoto et al., 2021).

Moreover, resistance training can also improve cognitive functioning (Landrigan et al., 2020); single bouts of resistance exercise showed more significant improvements when higher loads were used (Chang and Etnier, 2009). However, the optimal exercise and training characteristics to effectively enhance cognitive functioning with chronic PE programs are relatively unknown (Soga et al., 2018). So, it seems that a single bout of both high-intensity aerobic or resistance exercise can acutely improve RT. However, we do not know if high-intensity exercise would also be effective when applied in chronic PE programs. It is possible that continuous exposure to lactate, in turn, could induce the release of BDNF to produce such an effect (Hashimoto et al., 2021).

Regarding changes in cognitive functioning, PT and acute PE have been shown to improve attention processes, information processing speed, and executive control (Colcombe and Kramer, 2003; Tsai et al., 2014; Pontifex et al., 2015). Among the various tools generally used to determine the impact of PE on the above-mentioned cognitive variables, RT has been used in the literature to evaluate cognitive and motor functions, as it involves both central and peripheral components (Ozyemisci-Taskiran et al., 2008). RT is understood as the time a person needs to initiate a movement (Magill, 2010). There are different types of RT. On the one hand, simple RT occurs when only one possible stimulus requires a single type of response (Posner and McLeod, 1982), whereas in more complex choice RT, there are different possibilities to choose from during the experiment, as it involves the appearance of different stimuli that require different responses (Neubauer, 1990). More specifically, RT measures processing speed (Mulder and van Maanen, 2013), and this variable reflects a person's cognitive functioning (Deary et al., 2010).

At the morphological level, processing speed may be an indirect measure of white brain substance, as changes in this substance are associated with changes in processing speed (Gunning-Dixon et al., 2009). At the behavioral level, it has recently been shown that medical students with better academic performance had lower RT (Prabhavathi et al., 2017). Not only that, in middle-aged and older people, lower performance in RT tasks can be a predictor of heart disease and stroke mortality (Shimizu et al., 2018).

Like in cognition, PA can improve wellbeing in young students (McMahon et al., 2017). Nowadays, wellbeing is a European priority (Miret et al., 2015), but there is no clear consensus about its definition or operationalization (Korhonen et al., 2014). Positive or negative indicators such as self-esteem, quality of life, positive and negative affect or vitality are usually used (Pastor et al., 2019). Some authors consider two perspectives for studying wellbeing: the hedonic perspective, which considers wellbeing as the presence of positive affect and the absence of negative affect; and the eudaimonic perspective, which associates wellbeing with the possibility of performing or expressing the most valuable human potentials, related to optimal psychological functioning (Ryan et al., 2013). Moreover, in both young and older individuals, it has been seen that cognitive performance changes could be affected by aspects such as mood and social relations (Lieberman et al., 2014). In addition, cardiorespiratory fitness (CRF) is related to vitality in young people (Eddolls et al., 2018), and vitality should correlate with positive and negative affect (Cervelló et al., 2014). Thus, the improvement of CRF with exercise training could improve wellbeing.

Consequently, it would be interesting to determine how PE can affect wellbeing and processing speed. At the acute level, improvements have been reported in complex RTs after sub-maximum exercise in university students (Audiffren et al., 2008; Ashnagar et al., 2015) and in adolescents' wellbeing (Pastor et al., 2019). On the other hand, some studies have observed a relationship between fitness and RT in young students (Luque-Casado et al., 2013; Wang et al., 2015; Maghsoudipour et al., 2018), although others did not find this association (Moradi et al., 2019). At the chronic level, the effects of the exercise intensity, duration, and frequency to produce long-term effects on processing speed and wellbeing in this population are not well-established.

Regarding exercise programs, the need to investigate new training methods to improve several fitness components simultaneously and efficiently, without high volumes of training and favoring adherence, has been indicated previously (Heinrich et al., 2014). In this sense, HIFT has recently emerged. HIFT is defined as a training style that incorporates various functional movements performed at high exercise intensity and is designed to improve general physical fitness and performance parameters (Feito et al., 2018). Unlike HIIT, this type of training combines aerobic activities with exercises to improve muscle strength (Feito et al., 2018). Among its benefits are improved body composition, power, muscle strength, and aerobic capacity, the same as or even more so than when performing continuous workouts or HIIT (Feito et al., 2018). However, the term "functional" may not be correct in this training style (Ide et al., 2021), as HIFT can be more clearly described as combined or concurrent training. Therefore, like a high-intensity aerobic and resistance-training regime, it seems a powerful candidate to improve RT and wellbeing in young people. Moreover, high-intensity exercise can release high amounts of lactate, a molecule positively related to cognitive function (Hashimoto et al., 2021).

Therefore, this study’s main objective was to determine whether a supervised HIFT group program of 10 weeks could improve processing speed and wellbeing. However, as a consequence of the COVID-19 pandemic, a national lockdown was announced in the middle of the program (week five), and supervised training had to be terminated. Thus, online training was implemented for the next 5 weeks.

The COVID-19 pandemic impacted the economy and society in many aspects, disturbing lifestyle and health behaviors (Dragun et al., 2021). The lockdown deteriorated daily activities, especially physical activities (Dragun et al., 2021). In addition, as a consequence of the quarantine, there was a negative impact on the population’s wellbeing (Brooks et al., 2020), with higher levels of anxiety and depression (Burke et al., 2020).

The study’s second objective arose as a consequence of the COVID-19 quarantine. We aimed to determine whether the “stay-at-home” orders and the need to continue training at home individually, adapting it to the new situation, would impact cognitive functioning and wellbeing in the participants.

Thus, we hypothesized that the 5-week HIFT supervised training phase would improve participants’ RT and psychological wellbeing and give rise to high adherence rates. Conversely, the phase carried out during the 5 weeks of strict quarantine due to COVID-19 was expected to decrease wellbeing compared to the in-person, supervised program, coupled with lower adherence and a reduction in RT improvement.

MATERIALS AND METHODS

Participants

The sample consisted of 42 college students, 21 in the experimental group (14 males and 7 females) and 21 in the control group (9 males and 12 females). All the participants were adults over 18 years old, and all of them claimed to be sedentary (one or fewer days of PE a week) during at least the last 6 months. In addition, all participants completed an initial questionnaire to ensure they met the requirements to be part of the study, such as not having recently suffered injuries and not being involved in any other training program. Their sociodemographic characteristics are summarized in Table 1.

Table 1. Anthropometric and fitness characteristics of the participants (*n* = 42)

Characteristics	Experimental (*n* = 21)	control (*n* = 21)
Age (years)	19.71 ± 1.71	21.52 ± 2.74
Weight (kg)	69.17 ± 8.04	66.57 ± 13.57
Height (m)	1.72 ± 0.09	1.69 ± 0.08
BMI (kg/m^2)	23.20 ± 2.25	23.20 ± 3.73
VO_2 max ($ml \cdot kg^{-1} min^{-1}$)	43.50 ± 5.42	
MAS (km/h)	14.20 ± 1.75	15.47 ± 2.91
HR max (beats · min^{-1})	200.90 ± 7.99	193.60 ± 8.16

All values are expressed as mean ± SD. Abbreviations: BMI, body mass index; VO_{2max}, maximum oxygen consumption; HR_{max}, maximum heart rate; MAS, maximal aerobic speed.

Measurements

Cardiorespiratory Function: Stress Test

Participants of the experimental group performed a maximum incremental test on a treadmill with a measure of oxygen consumption (VO_2) and heart rate (HR) throughout the test to determine the maximum VO_2 (VO_{2max}), maximum HR (HR_{max}), and their associated values in the first (VT1) and second ventilatory threshold (VT2). The exchange of respiratory gases was measured using the MasterScreen CPX analyzer (Hoechberg, Germany) breath by breath after being calibrated. The VO_2 max was calculated as the highest 30-s mean of VO_2. In addition, 15-s means of O_2 and CO_2 were used to determine VT1 and VT2 (Pettitt et al., 2013). Participants were not allowed to drink or speak during the test and were asked to refrain from intense exercise 24 h earlier.

The incremental test protocol consisted of a 3 min warm-up at 5 km/h with a 1% slope. Then, the test was performed on a 1% slope and began at a speed of 6 km/h and increased 1 km/h per minute until fatigue.

The incremental test protocol could not be repeated at the end of the study due to the COVID-19 lockdown, so no data regarding the possible fitness improvements of the participants was obtained.

Cognitive Functioning

Reaction Time

A test of increasing difficulty was used to measure the time required to respond to a stimulus. All the participants were requested to complete the test in the afternoon at home. The test was carried on a day with no exercise training session in a quiet place. A digital application with three tests was used in the study (AppAndAbout, 2019). Each test consisted of passing ten trials of different stimuli, and between each trial, there was a random rest period between 1,000 and 1,500 ms. The first test, the Training Test (TrT), was used to train the participants at the beginning of each measure. In the TrT, a green or red luminous stimulus was presented, and the subject had to press a green button only if the stimulus presented was of the same color. In the second test, the Choice Reaction Test (CRT) (ICC = 0.78, SEM = 0.05 s), there were also two luminous signals, red and green, and two buttons, red and green. The subject had to press the button with the matching color corresponding to the luminous signal presented (e.g., if the light signal was red, they had to press the red button). The third test, the Interference Test (InT) (ICC = 0.80, SEM = 0.05 s), consisted of introducing interference in the decision process of the second test: the participants had to respond in reverse, such that the signal should not coincide with the color of the button (e.g., if the light signal was green, they must press the red button). The third test was the most complex because it added interference. A familiarization protocol was used at the beginning of the study, repeating all tests five times. The familiarization protocols of the first 15 participants were analyzed to calculate the ICC of the tests, with moderate to strong reliability (Wells et al., 2014).

Psychological Wellbeing

Subjective Vitality

The Subjective Vitality Questionnaire (Ryan and Frederick, 1997) was used to measure the perception of vitality before and after the two phases of the training program, adapted to Spanish by Molina-García et al. (2007). This questionnaire can be considered a measure of psychological wellbeing (Ryan et al., 2013). This instrument comprises seven items that indicate how one feels at present (e.g., I feel alive and vital). The responses are rated on an eight-point Likert-type scale ranging from 0 (*not completely true*) to 7 (*very true*). Cronbach's alpha in the different experimental situations was comprised between 0.88 and 0.95.

Affective State

Following each training program phase, participants were asked to complete the *Positive and Negative Affect Schedule* (Mackinnon et al., 1999), which assesses their positive and negative feelings. This questionnaire is considered a hedonic measure of wellbeing. The scale is made up of nine adjectives, which are grouped into two factors in response to the item "Indicate how you feel right now…." Four of its items are associated with *Positive Affect* ("joyful, happy, content, amused") and five with *Negative Affect* ("depressed, worried, frustrated, angry, unhappy"). The responses are rated on an eight-point Likert-type scale ranging from 1 (*not completely*) to 7 (*extremely*). Cronbach's alpha for Positive Affect was between 0.89 and 0.95, and for Negative Affect between 0.83 and 0.92.

Adherence to the Training Program

Participation was monitored through a registration sheet in the supervised sessions and a mobile application during the quarantine phase. In addition, each person recorded the session and their perception of effort (RPE: rate of perceived exertion) 30 min after completing the session by the modified RPE-10 scale. A total of 30 sessions was performed, 15 in each of the phases of the program (supervised and online phases). Adherence was considered sufficient if at least 90% of the sessions were completed (Heinrich et al., 2014).

Procedure

The physical evaluation was carried out at the beginning of the program, and RT and wellbeing evaluations were conducted before the start of the training program (January–February 2020), after 5 weeks of the supervised group intervention (March 2020), and after 5 weeks of individual training during the quarantine period due to the COVID-19 global pandemic (April 2020). The experimental procedure for this study followed the latest (7th) Helsinki Declaration and was approved by the University Ethics Committee (UMH.CID.DPC.02.17). Study participants gave their informed written consent before participating in the study and were informed of the confidentiality and anonymity of the results obtained.

The participants' experimental allocation was distributed as is shown in the CONSORT flow chart (Figure 1). The inclusion criteria were (a) did not participate in any PE program simultaneously, (b) physical inactivity in the last 6 months, and (c) did not suffer injuries in the last 6 months. The participants were randomized using Microsoft Excel software with the "Random" function. There was no allocation concealment.

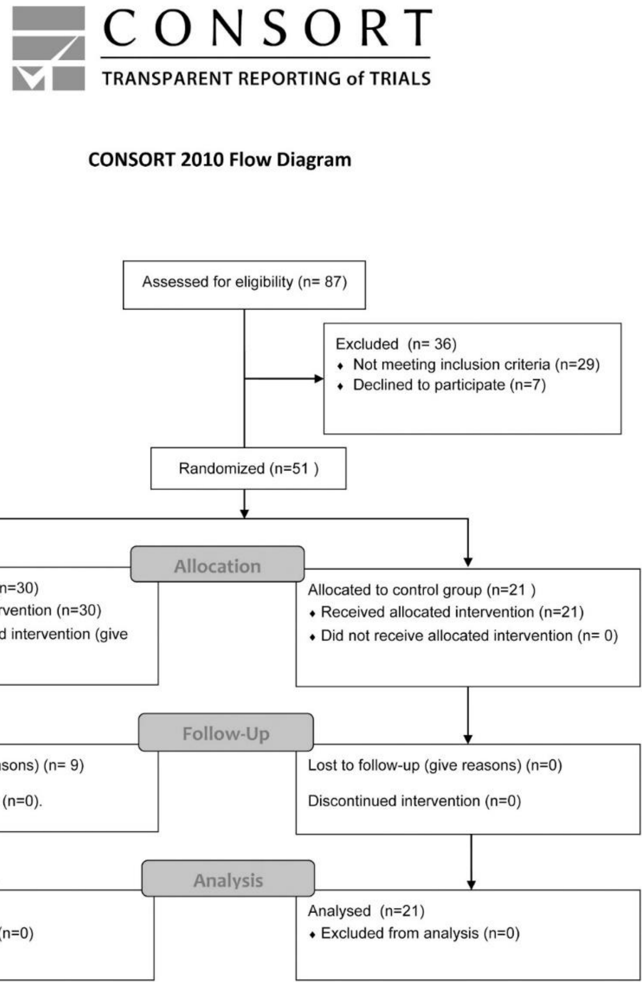

Figure 6. Consort flow chart.

The sample size was calculated *post-hoc* using G-Power (G*Power software, ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).[1] It was calculated for the RT analysis. For an ANOVA-RM 2 × 3, and with 42 participants, it is necessary an effect size of $\eta_p^2 > 0.04$ to ensure a statistical power (1–

β) > 0.8 (α = 0.05, correlation among repetitive measures = 0.45). Results have a positive power with $\eta_p^2 > 0.04$.

Training Program

Two research group members prescribed the supervised training program and carried it out. The sessions were 1 h long, 3 days a week (Monday, Wednesday, and Thursday). The sessions were conducted at university facilities, dividing the participants into two different time schedules to ensure the availability of the material. The training sessions during the quarantine phase were sent to participants *via* a mobile application to be performed at home.

The sessions were divided into four parts: (a) 10 min of a standardized warm-up; (b) a strength-block of about 15 min, occasionally, on a specific movement pattern with load requirements as a function of the manifestations of muscular endurance or hypertrophy depending on the week; (c) HIFT as the primary training block, which ranged from 10 to 30 min; and (d) cool down through mobility exercises and 10 min of static stretches. Repetition methods (completing a series of exercises in the shortest possible time, or maximum repetitions in a scheduled time) or time methods (rest-work ratios similar to the traditional HIIT method) were used in the main HIFT block. This block included cyclic exercises, such as running or jumping rope, and muscle endurance exercises with bodyweight or light loads (e.g., squats, swings, med ball throws, push-ups, pull-ups, jumps, and more) (Feito et al ., 2018). The exercise intensity was all-out for all, and the recovery was self-paced, self-selected, and passive (Feito et al., 2018). The training sessions were adapted to the new situation during the quarantine period. Thus, work with loads was prescribed using generic materials that anyone may have at home (bags of rice, bottles of water, milk containers, and other common materials) (Jiménez-Pavón et al., 2020). The days and hours of training were the same during the presential and quarantine periods.

Monitoring and Quantification of Training

The exercise intensity of the presential training sessions was rated with two different methods, one objective and one subjective: HR and subjective RPE-10 scale of the session. Only RPE was used during the sessions during quarantine.

Heart rate was registered during the sessions with the Polar Team2 Pro System (Polar Electro Oy, Kempele, Finland), which includes 20 coded chest straps, allowing HR registration every second. The recorded HR was used to calculate a load of each session, using Lucia's Training Impulse (TRIMPs) method (Lucía et al., 1999), which uses the HR at the individual ventilatory thresholds obtained in the stress test to establish three training zones: Zone 1 "below VT1," Zone 2 "between VT1 and VT2," and Zone 3 "above VT2." For the calculation of the TRIMP, the time expended in each zone is multiplicated by the zone number (1, 2, or 3).

The modified 10-point scale was used to quantify the internal load through the RPE (Foster et al., 2001). Participants were asked to determine the exercise intensity of the training 30 min after completing it.

Statistical Analysis

Repeated-measures ANOVA was performed, followed by a *post-hoc* test with Bonferroni adjustment to detect changes between the different time measurements for CRT, InT, positive affect, negative affect, vitality, and attendance. The bilateral significance level was set at $p < 0.05$. Sphericity was evaluated with Mauchly's sphericity test. The effect sizes are expressed as partial eta-squared (η_p^2) and are grouped as small (≤0.01), medium (≤0.06), and large (≤0.14) (Cohen, 1992). Paired *t*-test were used to analyze the exercise intensity of the sessions. A Pearson correlation was performed to analyze the relations of the wellbeing questionnaires. The results were analyzed with JASP 0.16 software (Eric-Jan Wagenmakers, Department of the Psychological Methods University of Amsterdam, Nieuwe Achtergracht 129B, Amsterdam, Netherlands).

RESULTS

Perception of effort was maintained with similar values during the online training sessions and the supervised training sessions (Figure 2). Moreover, during the supervised training sessions, the evolution of RPE was similar to LuTRIMP evolution (Figure 2). Despite changes in the structure of the sessions between the two phases, no significant differences in the exercise intensity of the sessions were observed through the recording of RPE between the supervised sessions and online sessions or between sessions (Figure 2), analyzed with paired *t*-tests ($p = 0.39$). Therefore, the stabilization of improvements in RT and the decrease in adherence between the two phases of the program were not attributable to load differences in the prescribed sessions, so there may be other underlying factors.

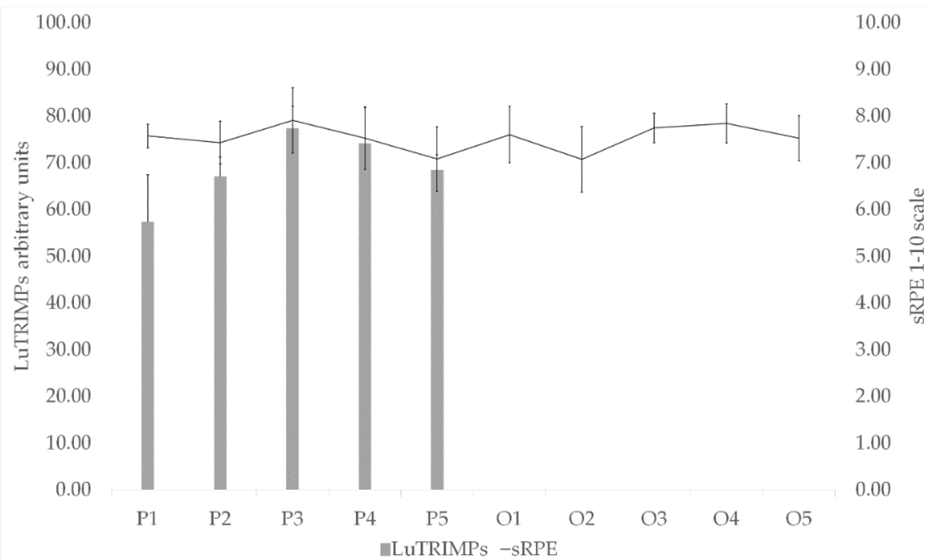

Figure 7. Weekly (1–5) load in presential sessions (P) and online sessions (O) during quarantine periods expressed in RPE and LuTrimp. n = 21.

The repeated-measures ANOVA shows the interaction between TIME at the three time points [pretest (PRE), after 5 weeks of supervised training (POST 5), and after 5 weeks of online training (POST 10)] and GROUPs [experimental group (exp), control group (con)].

For the CRT, the TIME x GROUP showed a significant difference with large effect size [$F_{(1,40)} = 3.602$, $p = 0.032$, $\eta_p^2 = 0.085$]. The *post-hoc* Bonferroni analysis showed an improvement only in the experimental group during the intervention [PRE vs. POST5: $M = 46.77$, $SD = 14.46$, $t_{(19)} = 3.23$, $p = 0.027$; PRE vs. POST10: $M = 59.93$, $SD = 14.47$, $t_{(19)} = 4.14$, $p = 0.001$] (Figure 3).

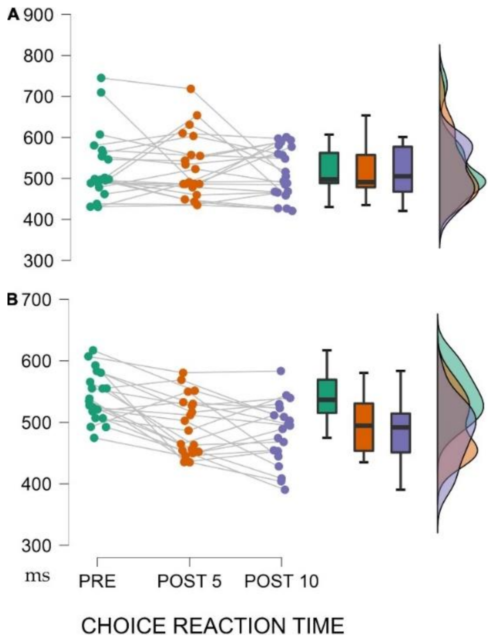

Figure 8. **(A)** Control Group. **(B)** Experimental Group. Evolution of CRT during the training process. At the beginning of the study (PRE), after 5 weeks of supervised training (POST 5) and after another 5 weeks of online training during quarantine (POST 10). Significant results shown with p-values are for the experimental group. Data are shown as mean ± standard error.

For the InT, the TIME x GROUP showed a significant difference with a large effect size [$F_{(1,40)} = 5.664$, $p = 0.005$, $\eta_p^2 = 0.124$]. Furthermore, the *post-hoc* Bonferroni analysis showed an improvement only in the experimental group during the intervention and only at the end of the 10-week training program [PRE vs. POST10: $M = 73.61$, $SD = 23.028$, $t_{(19)} = 3.19$, $p = 0.030$] (Figure 4).

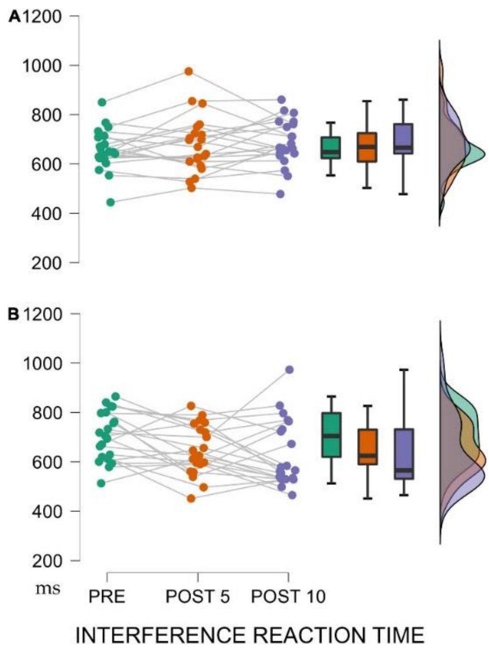

Figure 9. (A) Control Group. **(B)** Experimental Group. Evolution of InT during the training process. At the beginning of the study (PRE), after 5 weeks of supervised training (POST 5) and after another 5 weeks of online training during quarantine (POST 10). Significant results shown with p-values are for the experimental group. Data are shown as mean ± standard error.

There were differences in adherence to the sessions between the two periods (supervised vs. online). There was 94% adherence during the supervised period and 71% adherence during the lockdown. An RM ANOVA was done to compare the evolution of the five sessions developed under supervision and online (RM ANOVA 5 × 2, a repeated measure for sessions, and between-subject factor for supervised vs. online training). When we compared the attendance of the participants to the sessions, there was a significant reduction in adherence to the online program [$F_{(1, 58)} = 3.179$; $p = 0.014$; $\eta_p^2 = 0.052$]. The Bonferroni *post-hoc* analysis showed a significant reduction in attendance to session 3 [$M = 0.53$, $SD = 0.16$, $t_{(29)} = 3.31$, $p = 0.049$], 4 [$M = 0.53$, $SD = 0.16$, $t_{(29)} = 3.31$, $p = 0.049$] and 5 [$M = 0.83$, $SD = 0.16$, $t_{(29)} = 5.17$, $p < 0.001$] compared to the first online session (Figure 5).

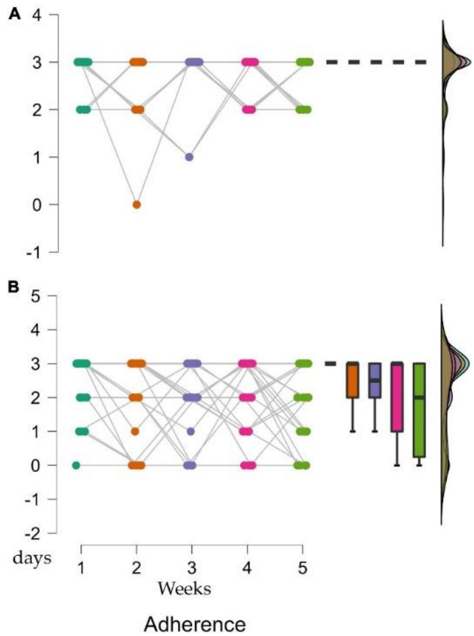

Figure 10. (A) Adherence during the supervised period. **(B)** Adherence during the online period. Weekly adherence in the supervised (weeks 1–5) and online (weeks 6–10) periods. Differences were only present during the online training period.

Finally, the effects of training on wellbeing were analyzed, taking into account three variables (positive affect, negative affect, and subjective vitality). The analysis was done for the three temporal moments (PRE, POST 5, POST 10) and the two groups (experimental vs. control group). The repeated-measures ANOVA revealed the absence of significant differences for the three variables, positive affect [$F_{(1, 40)} = 2.34$, $p = 0.11$, $\eta_p^2 = 0.11$], negative affect [$F_{(1, 40)} = 0.21$, $p = 0.979$, $\eta_p^2 = 0.001$], and subjective vitality, [$F_{(1, 40)} = 0.88$, $p = 0.42$, $\eta_p^2 = 0.04$]. Therefore, the results show that neither the supervised nor the online training phase affected wellbeing. Moreover, we saw a strong correlation between the three variables in the population (Table 2).

Tabla 2. Correlations between wellbeing variables.

	Variable	Positive affect	Negative affect	Vitality
Pearson's correlations in PRE				
Negative affect	*n*	42	–	
	Pearson's r	−0.578***	–	
	p-value	<0.001	–	
Vitality	*n*	42	42	–
	Pearson's r	0.665***	−0.463**	–
	p-value	<0.001	0.002	–
Pearson's correlations at POST 5				
Negative affect	*n*	41	–	
	Pearson's r	−0.531***	–	
	p-value	<0.001	–	
Vitality	*n*	41	41	–
	Pearson's r	0.797***	−0.551***	–
	p-value	<0.001	<0.001	–
Pearson's correlations at POST 10				
Negative affect	*n*	42	–	
	Pearson's r	−0.367*	–	
	p-value	0.017	–	
Vitality	*n*	42	42	–
	Pearson's r	0.712***	−0.349*	–
	p-value	<0.001	0.024	–

**p* < 0.05, ***p* < 0.01, and ****p* < 0.001.

All the analyses were repeated considering the participant's sex, and no differences were found in any variable in the TIME × GROUP × SEX analysis [CRT $F_{(3,37)} = 0.431$, $p = 0.65$, $\eta_p^2 = 0.01$; InT $F_{(3,37)} = 0.274$, $p = 0.76$, $\eta_p^2 = 0.007$; Positive Affect $F_{(3,37)} =$

1.54, $p = 0.22$, $\eta_p^2 = 0.04$; Negative Affect $F_{(3,37)} = 1.58$, $p = 0.21$, $\eta_p^2 = 0.04$; Vitality $F_{(3,37)} = 0.783$, $p = 0.46$, $\eta_p^2 = 0.02$].

DISCUSSION

The objective of this study was to determine whether HIFT could improve cognitive functioning, measured as complex RT, and wellbeing, measured as vitality and positive and negative affects, in young college students. Although the participants declared a sedentary lifestyle during the previous 6 months of the study, their VO_2 max were within the normative values provided in the literature (Dwyer et al., 2005). As a result of the COVID-19 lockdown, a second objective, to analyze these variables and adherence during a quarantine period with online training, was included.

Regarding the participants' processing speed, we observed that 5 weeks of HIFT supervised training improved their RT (CRT and InT). Our findings are in accordance with the literature, providing moderate to strong evidence that exercise being performed at moderate to vigorous exercise intensity can improve processing speed (Erickson et al., 2019).

The different neurophysiological mechanisms that underlie such functional changes might explain the benefits of chronic PE for processing speed. For example, angiogenesis and neurogenesis are structural brain changes mediated by exercise (van Praag et al., 2005). BDNF has been shown to be an essential neurotrophin in this process (Notaras and van den Buuse, 2019). In this sense, a previous study observed that a 3-month HIFT program significantly increased resting BDNF levels in young adults (Murawska-Cialowicz et al., 2015). The chronic changes in the brain must be differentiated from the acute effects. It seems that the benefits of exercise on complex

RT may, as an acute response, be mediated by transient phenomena such as the release of catecholamines at the central level (Meeusen and De Meirleir, 1995), which modulate information processing (Robbins and Everitt, 1995).

However, we still do not entirely understand the mechanism related to cognitive improvement (Stillman et al., 2020). In this way, Stillman et al. (2016) proposed a multilevel system to study the underlying changes in cognitive functioning. Thus, cognitive changes can be produced by (a) molecular and cellular modifications (level 1), (b) structural and functional brain changes (level 2), and (c) behavioral and socioemotional changes (level 3). However, traditionally, the literature has focused on the first two levels, and there is a lack of evidence to understand the relations between behavioral and socioemotional changes with cognitive functioning (Stillman et al., 2016). Therefore, our study aimed to analyze the relationship between cognitive functioning and wellbeing, focusing on level 3 changes. Our hypothesis considered that hedonic and eudemonic variables of wellbeing would improve together with the RT variables.

However, the study results show that neither a 5-week HIFT supervised training program nor the online training during the COVID-19 quarantine affected this variable. Regarding the effect of training on these variables, the data contradict previous reports in the literature where acute, chronic PE and PT have been considered an effective tool to improve the wellbeing of young students (Cervelló et al., 2014; Garcia et al., 2015; Eather et al., 2019). However, some studies have found that high-intensity training did not cause significant changes in the wellbeing of this same population (Costigan et al., 2016). Moreover, data suggests an attenuated impact of the COVID-19 quarantine on the wellbeing variables in young students who presumably would not be burdened with responsibilities to the same degree as the adult population and thus experience less emotional distress (Brooks et al., 2020).

It has been shown that changes in cognitive functioning could be influenced by aspects of supervised training linked to mood and social relationships [could be related to level 3, as was proposed by Stillman et al. (2016)], such as (a) creating a structured and collaborative environment that favors positive reinforcement by peers and coaches; (b) a positive perception of social support; (c) achievement of goals; and (d) positive group dynamics (Lieberman et al., 2014). In agreement with these studies, our cognitive functioning improvements were higher during the supervised training than during the online training. However, improvements in processing speed were sustained through online training during the lockdown, unaffected by the reduction in adherence and social interactions. PE was probably sufficient to maintain unaltered mood and wellbeing, and the changes in processing speed could have been mediated by level 1 and 2 mechanisms (Stillman et al., 2016).

Although wellbeing was not modified due to the lockdown, significant differences in adherence were observed between the supervised and online phases. Self-determination theory (SDT) can explain the decrease in adherence (Deci and Ryan, 1985, 2000). SDT describes three psychological needs (autonomy, competence, and relatedness) that must be satisfied to increase the intrinsic motivation for a given activity. In our online training program, some of these needs were not satisfied, such as relatedness (Deci and Ryan, 1985) with peers and coaches, which has a significant impact on adherence to exercise (Kang et al., 2019), or the supervision of qualified professionals (Garber et al., 2011). In addition, recent studies have shown that people who reduced their PA during lockdown experienced decreased wellbeing (Brand et al., 2020; Faulkner et al., 2021). However, in our results, despite the correlation between positive and negative affect with vitality, the latter was not reduced in parallel with a decrease in adherence. Moreover, CRF is related to vitality in young people (Eddolls et al., 2018), and CRF can be maintained with a lower volume of exercise if the intensity of the activity is conserved (Spiering et al., 2021). Given that there were no changes in the exercise intensity throughout the training program, the reduction in adherence in this study probably did not affect CRF, and hence, vitality was not altered.

Our study demonstrates that HIFT can improve cognitive functioning in young university students and could be successfully applied through online training under lockdown circumstances, maintaining the exercise intensity and improving cognitive functioning. Moreover, as we have demonstrated, it is possible to maintain the subjective exercise intensity (measured by RPE) of the HIFT training in the online approach, with no adverse changes in wellbeing. However, if we want to use this methodology in future lockdowns, it would be interesting to analyze the lockdown training protocols from the SDT perspective, trying to overcome psychological needs deficiencies during the quarantine periods.

Finally, our study did not find any sex differences in the analyses performed. A previous meta-analysis showed discrepancies in sex differences. For example, Barha et al. (2017) found that sex was a strong moderator in the exercise-cognition relationship in their meta-analysis, with more pronounced improvements for women. However, Falck et al. (2019) did not find this relationship in their meta-analysis. In any case, both meta-analyses were done in older people. Some old studies showed that older women participated in lower leisure-time PA than older men (Lee, 2005), or reported lower frequencies of physical activities (Kaplan et al., 2001). In addition, sedentarism has a worse cognitive impact in women than in men (Fagot et al., 2019). Thus, Barha and Liu-Ambrose (2018) proposed that the increase in daily PA could be greater for older women than for older men, and this difference could promote more significant cognitive improvements in women. However, recent studies have shown that, nowadays, older women are less sedentary and do more PA than men (Wennman et al., 2019; Lopez-Valenciano et al., 2020). Suppose PA determines the cognitive functioning improvements after a PT period. In that case, present and future research will find a sex gap with better improvements in older men.

Regarding this study, we do not know any review of sex differences in young university students on the exercise-cognition relationship. Thus, according to the results of our study, sex does not moderate the improvement in processing speed after chronic exercise in young people.

This study investigated whether, in young adults, supervised and unsupervised HIFT can influence wellbeing and cognitive functioning, as empirical evidence regarding the effect of PEs on wellbeing and cognitive functioning is scant in this age group (Stillman et al., 2020). However, we did not find evidence that exercise-related changes in socioemotional parameters are associated with alteration of cognitive functioning, as previously proposed (Stillman et al., 2016). We described our training methodology with HR records and used ventilatory thresholds to control the exercise load. The implications that arise from the findings of our study broaden our knowledge on the influence of HIFT on cognitive functioning and wellbeing in younger adults.

Limitations

As a result of lockdown, the main limitation to this study was that it was impossible to carry out post-training fitness tests, so we do not know if the observed changes in cognitive functioning are related to improvements in fitness. Therefore, it would be interesting for future research to look into the implicit mechanisms related to physical fitness that could potentially explain improvements in complex RT. Moreover, the study did not employ allocation concealment, which indicates a possible source of bias.

CONCLUSION

On the one hand, HIFT training improves processing speed, measured through two complex RT tasks (CRT and InT) in young college students, without mediation by changes in psychological wellbeing. Also, it was observed that a training program during a quarantine period, forced by the global COVID-19 pandemic, promoted the maintenance of RT improvements previously achieved during a supervised training program. On the other hand, it was observed that this situation did not have adverse effects on this population's wellbeing. However, it negatively affected adherence to the online training program, possibly because of the suppression of typical factors linked to training supervision and interactions with peers and coaches.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Miguel Hernández University Ethics Committee (UMH.CID.DPC.02.17). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB-F, LC-H, DP, and EC contributed to the conception and design of the study. JB-F organized the database. JB-F, LC-H, and DP performed the statistical analysis and wrote the final manuscript. JB-F and LC-H wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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CONFLICT OF INTEREST

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.

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ANEXO 2

ESTUDIO AGUDO 1

Effect of acute exercise intensity on cognitive inhibition and well-being: Role of lactate and BDNF polymorphism in the dose-response relationship.

Nota. Este estudio se encuentra publicado.

Ballester-Ferrer JA, Bonete-López B, Roldan A, Cervelló E and Pastor D (2022) Effect of acute exercise intensity on cognitive inhibition and well-being: Role of lactate and BDNF polymorphism in the dose-response relationship. *Front. Psychol*. 13:1057475. doi: 10.3389/fpsyg.2022.1057475

8.2. Anexo 2

8.2.1. Estudio agudo 1. Effect of acute exercise intensity on cognitive inhibition and well-being: Role of lactate and BDNF polymorphism in the dose-response relationship.

Abstract

There is evidence in the literature that acute exercise can modify cognitive function after the effort. However, there is still some controversy concerning the most effective exercise modality to improve cognitive function in acute interventions. Regarding these different exercise modalities, the dose–response relationship between exercise intensity and cognitive response is one of the most challenging questions in exercise and cognition research. In this study, we tested the impact of moderate-intensity (MICT), high-intensity (HIIT) exercise sessions, or control situation (CTRL) on cognitive inhibition (measured with the Stroop Test). Thirty-six young college students participated in this study, where a within-subject repeated measure design was used. ANOVA 2×3 demonstrated that HIIT improved the acute cognitive response to a higher degree when compared to MICT or CTRL ($p < 0.05$). The cognitive improvements correlated with lactate release, providing a plausible molecular explanation for the cognitive enhancement ($r < -0.2$ and $p < 0.05$ for all the Stroop conditions). Moreover, a positive trend in wellbeing was observed after both exercise protocols (HIIT and MICT) but not in the CTRL situation. Genetic BDNF single nucleotide polymorphism did not influence any interactions ($p < 0.05$). In this sense, our results suggest that exercise intensity could be a key factor in improved cognitive function following exercise in young college students, with no additional impact of BDNF polymorphism. Moreover, our results also provide evidence that exercise could be a useful tool in improving psychological wellbeing.

Keywords: *cognitive inhibition, exercise, wellbeing, lactate, BDNF*

INTRODUCTION

Learning is a higher-order process emerging from the Central Nervous System and shaped through the interaction of diverse cognitive domains; among them, executive function (EF) plays a central role (Diamond, 2013). EF is a broad term that comprises a set of neurocognitive skills necessary for optimal daily functioning, academic success, and employability (Diamond, 2013; Titz and Karbach, 2014). These skills include inhibitory control (or simply inhibition), working memory, and cognitive flexibility (also termed mental set shifting; Diamond, 2013). Given the importance of the said skills across the lifespan, strategies for their optimization have been extensively explored in the literature. Physical exercise has emerged as one of the most promising tools to benefit all aspects of executive function (Chang et al., 2012; Stillman et al., 2016; Oberste et al., 2019; Pontifex et al., 2019; Stillman et al., 2020). Of all of them, Inhibitory control is the most studied domain out of the three core EFs in its relationship to the effects of acute physical exercise (Pontifex et al., 2019). Inhibitory control refers to the capacity of an individual to override strong impulses and focus attention on relevant stimuli, thus, ensuring goal-oriented behaviors (Nigg, 2000; Friedman and Miyake, 2004). Although a large body of research has focused on the benefits of physical exercise on cognition in general and inhibition in particular, evidence examining the underlying mechanisms is still lacking (Stillman et al., 2016, 2020).

The dose–response relationship of both acute and chronic exercise has gained attention as an easily modifiable moderator variable in the exercise-cognition literature (Chang et al., 2012, 2015; Herold et al., 2019; Oberste et al., 2019; Ludyga et al., 2020). Evidence suggests that as long as a rest interval is introduced after a single bout of aerobic exercise, higher intensities should result in larger improvements in cognition (Chang et al., 2012; Oberste et al., 2019). Along the same lines, exercise intensity was shown to modulate the exercise response-inhibition relationship, with high-intensity interval training (HIIT) producing superior results, followed by vigorous continuous exercise. Conversely, only a small benefit was reported for moderate continuous training (MICT) compared to a no-exercise control condition (Oberste et al., 2019). In an attempt to elucidate the underlying mechanisms of the findings above and expand our knowledge of the exercise-cognition relationship, the vast majority of the studies have focused on molecular and cellular interactions and structural and functional cerebral changes (Stillman et al., 2016). In this line of evidence, high-intensity exercise was shown to prompt the release of neurotrophic factors, such as Brain-Derived Neurotrophic Factor (BDNF; Saucedo Marquez et al., 2015). The implication is that BDNF mediates cognitive enhancement following acute exercise, and this relationship, in turn, could be related to lactate production (Ferris et al., 2007). In fact, recent studies have demonstrated that lactate released from the exercising muscle during a high-intensity bout could cross the brain–blood barrier (El Hayek et al., 2019; Nicola and Okun, 2021) and induce BDNF expression in the brain (Müller et al., 2020). Lactate, thus, has been proposed as a key molecule in brain health and the observed cognitive enhancement following physical exercise (El

Hayek et al., 2019; Hashimoto et al., 2021). However, some studies have suggested the inverted U-shaped relationship between exercise and cognition. According to this theory, moderate-intensity exercise protocols granted the most cognitive gains rather than those that incorporated exercise of lighter or higher intensities (Pontifex et al., 2019).

It has been argued that molecular and cellular modifications alone cannot explain the exercise-cognition relationship, and other socioemotional and behavioral aspects could be implicated, but the literature concerning social and behavioral aspects is scarce (Stillman et al., 2016). In this regard, exercise could improve psychological wellbeing (Cervelló et al., 2014). At the same time, psychological wellbeing is viewed as a modulator of the learning process, with previous research highlighting its central role in academic achievement in young students (Garcia et al., 2015; Yu et al., 2017). Moreover, some studies have hypothesized that low cognitive performance could affect psychological wellbeing, leading to mental health issues in the present or in the future (Leahy et al., 2020), and although there is still no agreement on what defines psychological wellbeing (Korhonen et al., 2014), a few perspectives on its study have come to light (Ryan et al., 2013). The hedonic perspective interprets wellbeing as the presence of positive affect and the absence of negative affect. In contrast, the eudemonic perspective associates wellbeing with an individual's ability to experience and exercise their human potential to achieve optimal psychological functioning (Ryan et al., 2013). Thus, understanding the benefits of physical exercise on cognition and psychological wellbeing, as well as the underlying pathways, could be of great importance for the integral health of the population.

In addition to modifiable factors mentioned above that were implicated in the cognitive response to exercise, other non-modifiable aspects, such as genetic profile, could potentially affect the individual response (Canivet et al., 2015). In this regard, levels of BDNF, a protein that mediates the effects of exercise on the brain and, by extension, on cognition (Cotman et al., 2007), have been reported to increase following exercise bout in an intensity-dependent manner (Ferris et al., 2007). Nonetheless, there is evidence that some individuals may not see the exercise-induced rise in BDNF, given precisely their genetic profile. In this respect, the BDNF gene regulates the release of BDNF; the single nucleotide polymorphism (SNP) of the gene, called SNP rs6262 or BDNF Val66Met gene polymorphism, substitutes a valine (Val) for methionine (Met) at codon 66. Those with methionine (Met/Met) polymorphism respond with lower BDNF levels to exercise (Egan et al., 2003); this observation could explain the reduced effects of exercise on cognition in these individuals (Canivet et al., 2015). Nonetheless, contrasting hypotheses exist on the relationship between cognitive response and BDNF polymorphism (de Las Heras et al., 2022). Some studies have reported a better cognitive performance in the Val carriers following exercise, compared to the Met carriers, given that the Val polymorphism is associated with higher activity-dependent BDNF release (Mang et al., 2013). On the other hand, some authors have proposed that activity-dependent BDNF secretion is less efficient in the presence of the methionine SNP, and thus, engagement in physical exercise, which should produce a rise in BDNF levels, would ultimately lead to an improved cognitive response in the Met carriers, rather than those with the valine SNP (Moreau et al., 2017). In Spain, the Val genotype is the most common (65.6–53.3%), followed by the Val/Met polymorphism (33.3–30.7%), and finally, the Met/Met genotype (13.3–3.7%; Combarros et al., 2004; Sánchez-Romero et al., 2009). Given these divergent theories, it appears necessary to advance our understanding of the implications of BDNF SNPs for an individual cognitive response.

For all the above reasons, the study's main objective was to explore the impact of exercise intensity on inhibitory control and psychological wellbeing. Moreover, we have also hypothesized that lactate released during exercise bout would be associated with Post-exercise cognitive enhancement, and genetic profile, such as BDNF polymorphism, would mediate cognitive response following exercise. In this regard, we have hypothesized that the participants with at least one Met allele would experience reduced exercise effects on their cognitive function.

MATERIAL AND METHODS

Subjects

Thirty-six university students (19 female subjects) were enrolled in the study. The sample size was estimated using G-Power for a ANOVA RM 2×3 repeated measures (1 group, 6 measures), where alpha was 0.05, power was 0.8, and the estimated $n_p^2 > 0.05$ was assumed. Given the variables of interest, we estimated that the required sample size should include 33 participants. Thirty-six participants were recruited to account for possible dropouts. In a *post hoc* analysis, the ANOVA RM showed a η_p^2 of 0.37 (congruent condition), 0.13 (neutral condition), and 0.19 (incongruent condition), meaning our study's power was > 0.99 in all conditions. Subjects were also asked to fill in the "Physical Activity Readiness Questionnaire" (PAR-Q) to ensure that neither of them had any contraindications to participating in an exercise protocol. Participants were asked to sign the informed written consent form prior to their inclusion in the study. The study protocol was guided in the most recent (7th) Declaration of Helsinki and was approved by the University Ethics Committee (UMH.CID.DPC.02.17). The characteristics of the participants are summarized in Table 1.

Table 1. Sample description.

Variable	Characteristics
Age (years)	21.97 ± 2.56
Height (m)	1.69 ± 0.09
Weight (kg)	70.07 ± 11.26
BMI (kg.m^2)	24.39 ± 2.72
Fat mass (%)	22.49 ± 7.13
HR_{max} (bpm)	196.56 ± 8.03
MAS (km/h)	14.95 ± 1.41

All values are expressed as mean ± SD. Abbreviations: BMI, body mass index; HR_{max}, maximum heart rate; MAS, maximal aerobic speed

Measurements

Cognitive function

Stroop test

The Stroop test (Stroop, 1935) is one of the most widely used neuropsychological instruments to assess several core cognitive processes, including executive function, selective attention, and inhibitory control (Golden, 1994; Chang et al., 2015, 2019). In our study, a digital version of the test was applied (Stroop test UMH-MEMTRAIN by Pastor et al., 2018), which allowed the assessment of reaction time and accuracy, following the original protocol described by Golden (1994). Eight-inch tablets (Lenovo TB3-850F) were provided to the participants to complete the test. The test comprises three stages of increasing difficulty. The first one represents a congruent condition, the second one represents the neutral condition, and the third trial is "incongruent" for the reasons detailed below. During each trial, one of four stimuli (the words "red," "blue," "yellow," or "green" in its Spanish translation or "XXXX") is displayed in the center of a screen on a white background. Meanwhile, the bottom of the screen features 4 buttons with the 4 possible answers in black ink (Spanish names for red, blue, yellow, or green) for each of the test conditions. In the first congruent condition, the color names (Spanish names for red, blue, yellow, or green) appear on the screen in black ink, and the subjects must match the word to the color it denotes from the bottom four options. Meanwhile, in the second neutral condition, rather than the color name, "XXXX" is displayed in any color ink mentioned earlier.

During the third incongruent condition, yet again the color name appears on the screen, but the color name does not correspond to the color ink of the word (i.e., the word “red” appears in green ink). In this case, the participants should respond to the color of the ink, rather than the the meaning of the word. Participants were instructed to select the correct option “as quickly and accurately as possible.” Each condition lasts 45 s, where the number of correct and incorrect answers is recorded. The test pauses for 25 s before starting the next condition. The dependent measurements are divided into three levels: (1) Congruent condition, (2) Neutral condition, and (3) Incongruent condition. Prior to the experimental condition, five familiarization trials of the Stroop task were carried out to reduce the learning effect. For the main analysis, reaction times and response accuracy were included. In our study, before starting the experimental protocol, we found the intraclass correlation coefficient (ICC) of reaction time in each of the conditions of the Stroop test (congruent: ICC = 0.76; neutral: ICC = 0.76; incongruent: ICC = 0.79) was high (>0.70; Rodríguez Barreto et al., 2016).

Stroop test check

Interactions between all three test conditions and three experimental protocols were analyzed to ensure adequate manipulation of the Stroop test. When the test is administered correctly, the incongruent condition should be perceived as the most complex compared to the two preceding conditions, independent of the external factors surrounding the test’s administration. As a consequence, ANOVA should reflect longer reaction times and worse precision rates in the incongruent condition before and after any experimental protocol. The drop-off in precision in the incongruent condition should also be similar between treatments.

The Pre-and Post-measurements of the Stroop test, for both reaction times and precision, were analyzed using ANOVA RM 3 × 3 (Congruent, Neutral, Incongruent × HIIT, MICT, CTRL).

For the reaction times, a main effect of the Stroop condition was demonstrated both in the Pre [$F_{(1.43, 48.71)} = 207.102$, $p < 0.001$, $\eta_p^2 = 0.86$] and in the Post [$F_{(1.44, 50.27)} = 169.28$, $p < 0.001$, $\eta_p^2 = 0.83$]. The same main effect (Stroop condition) was true for precision in both, the Pre [$F_{(2, 66)} = 10.98$, $p < 0.001$, $\eta_p^2 = 0.25$] and the Post [$F_{(1.64, 54.37)} = 6.91$, $p < 0.01$, $\eta_p^2 = 0.17$].

Moreover, the main effect of Treatment could not be demonstrated at either time point for precision rates ($p > 0.05$). For reaction times, on the other hand, although no effect of the Treatment was observed in the Pre ($p > 0.05$), it was found in the Post ($p < 0.05$).

Consequently, the incongruent condition resulted in the longest reaction times and the highest rate of precision errors when contrasted with the two remaining conditions (congruent and neutral). This finding agrees with those previously reported and is associated with the so-called Stroop effect (Mac Leod, 1991; Milham et al., 2002; Chang et al., 2019). It is worth highlighting that the precision ratios were similar between experimental protocols (HIIT, MICT, and CTRL). This latter observation, combined with the differences between Stroop conditions, indicates satisfactory manipulation of the Stroop test from our side.

Psychological wellbeing

Subjective vitality

The Subjective Vitality Questionnaire (Ryan and Frederick, 1997) was used to measure the perception of vitality before and after each experimental condition, adapted to Spanish by Molina-García et al. (2007). This questionnaire is considered a measure of psychological wellbeing (Ryan et al., 2013). The scale allows participants to express present-day feelings through seven items (e.g., I feel alive and vital). Responses are rated on an eight-point Likert-type scale ranging from 0 (not completely true) to 7 (very true). Cronbach's alpha in the different experimental situations was comprised between 0.76 and 0.92.

Affective state

Before and after each experimental situation, participants were asked to complete the Positive and Negative Affect Schedule (Mackinnon et al., 1999), to assess their positive and negative emotional experiences. This questionnaire is considered a hedonic measure of wellbeing. The scale is made up of nine adjectives grouped into two factors. The subjects chose those adjectives, which allowed them to respond to the following sentence: "Indicate how you feel at this moment…." Four of the items are associated with Positive Affect ("cheerful, happy, contented, amused") and five with Negative Affect ("depressed, worried, frustrated, angry, unhappy").

The instrument uses an eight-point Likert scale, ranging from 1 “not at all” to 8 “extremely.” Cronbach’s alpha ranged between 0.74 and 0.96 for the two factors in the present study.

Ramp incremental test

A graded exercise test on a treadmill was performed to establish Maximum Aerobic Speed (MAS); the latter was then used to calculate the relative intensities (i.e., speed) of both experimental conditions. The protocol included a 3-min warm-up at 5 km/h, followed by 1 km/h increments per minute until volitional exhaustion. A treadmill incline was set at 1% for both the warm-up and incremental stages. Heart rate (HR) was monitored throughout the test through H7 chest straps (Polar Electro Oy, Kempele, Finland) and allowed to register the maximum HR achieved by the end of the test. Participants were asked not to engage in any strenuous exercise 24 h prior to the test.

Intensity parameters

To determine blood lactate concentrations, samples were obtained from the participants’ earlobes 3 and 15 min after each of the experimental conditions. A portable lactate analyzer (Lactate Scout, SensLab GmbH, Germany) was used to employ the said evaluation.

HR was monitored during HIIT and MICT by means of H7 chest straps linked to the Polar Beat app (Polar Electro Oy, Kempele, Finland). The HR register was also utilized to ensure the participants adhered to the relative intensity corresponding to each experimental condition.

Genetic analysis

Saliva samples were collected with OrageneTM DNA Saliva Collection Kit (DNA Genotek S.L.). DNA extraction protocol was provided by the manufacturer. The sample was further analyzed using a quantitative real-time StepOne PCR of the Applied Biosystem, following the protocol of Sánchez-Romero et al. (2009).

Procedure

A within-subjects repeated measure design was employed, where the subjects completed the three experimental conditions (HIIT, MICT, and CTRL), 1 week apart, following a randomized, counterbalanced order. Before the experimental protocol, 1 week earlier, the subjects visited the laboratory to complete the Pre-participation questionnaires, familiarize themselves with the cognitive test in order to prevent a possible "learning effect," and provide saliva samples for genetic analysis. On the same day, the subjects also performed cardiorespiratory evaluation, with the data from the latter used to establish exercise intensities for both experimental conditions. Related to cognitive test familiarization, the participants performed a minimum of 5 attempts of each Stroop condition. The learning stabilization was considered when participants made two consecutive attempts with inter-trial variability below 5% in each condition (mean ± SD = 2.86 ± 1.11 between trials). Thus, we respected individual variability in learning the test. Prior studies have also used this percentage of intra-variability as an indication of stable performance in cognitive inhibition tests (Schmit et al., 2015; Pastor et al., 2021). At the same time, participants were also given the order of the experimental sessions as per counterbalancing technique, avoiding the possible influence of session order (Thomas et al., 2015). All visits were scheduled to begin at 9:00 a.m. Caffeine use was restricted, and water consumption was limited to 30 min prior to the visit on the day of saliva sample extraction, following the kit's manufacturer recommendations.

The experimental conditions (HIIT, MICT, and CTRL) were separated by 1 week. Each one took 20 min to be completed. The cognitive Stroop task and measures of wellbeing and affective state were assessed before and 15 min after the experimental and control conditions, always in the same conditions (same room, table, and chair). Blood lactate was measured before the exercise protocol, 3 min post-exercise, right after the cooldown to estimate the exercise intensity, and 15 min post-exercise was over and cognitive function assessment was about to begin. Subjects in the control condition remained seated while watching a video of general interest. Conversely, both exercise protocols included a 3-min warm-up at 60% MAS, but for the MICT session, participants were required to sustain this running speed until the completion of 20 min of exercise. The HIIT session consisted of 4 bouts of 2 min, with each bout performed at 95% MAS. Two minutes of passive recovery separated high-intensity efforts, while a 3-min cooldown followed the last bout. As with MICT, the entire protocol took 20 min to complete, making the volume of both exercise conditions standardized. The said volume was selected given the previous evidence suggesting that cognitive function, particularly executive control, may see the largest improvements after exercise sessions of similar duration (Chang et al., 2012; Oberste et al., 2019).

Data analysis

Several sets of analyzes were performed. For all of them, alpha was set at 0.05. Paired *t*-tests and RM ANOVA were used to analyze HR and blood lactate in all three conditions (HIIT, MICT, and CTRL) to ensure adequate manipulation of exercise intensity. For the main analysis of the dependent measures, repeated-measures analysis of variance (ANOVA RM) was calculated to assess differences in both cognitive functions (reaction times and response accuracy in the Stroop test) and psychological wellbeing (subjective vitality and states of positive and negative affect). If the sphericity assumption was not met, Greenhouse–Geisser corrections were applied.

To evaluate the response in the Stroop test, an ANOVA RM 2×3 (Time: Pre-Post × Treatment: HIIT, MICT, and CTRL) were performed for each Stroop Condition. ANOVA RM 2×3 tests (Time × Treatment) were carried out separately for Subjective Vitality, Positive affective state, and Negative affective state.

Additional separate analyzes were conducted for BDNF polymorphism using repeated-measures ANOVA RM with BDNF polymorphism (val/val, val/met or met/met) as a between-subjects factor to establish possible differences in the cognitive response based on the individual's polymorphism.

Paired *post hoc t*-tests with Bonferroni adjustments for multiple comparisons were performed to identify significant results in ANOVA analysis. As an assessment of effect sizes, partial squared eta (η_p^2) and Cohen's d were calculated. The effect sizes are grouped for η_p^2 as small (≤0.01), medium (≤0.06), and large (≤0.14) and for Cohen's d as small (≤0.20), medium (≤0.50) and large (≤0.80; Cohen, 1992).

Finally, Pearson's correlation analyzes (r) were performed to establish possible associations between changes (Δ) (Post-value – Pre-value) in blood lactate and changes in Stroop Test reaction time and between changes in wellbeing and changes in Stroop Test reaction time. The results were analyzed with JASP 0.16 software (Eric-Jan Wagenmakers, Department of the Psychological Methods University of Amsterdam, Nieuwe Achtergracht 129B, Amsterdam, Netherlands).

RESULTS

Exercise intensity parameters

The HR recording revealed higher values for HIIT than MICT both at an absolute level (164.7 vs. 153.1 bpm, $p < 0.01$) and at a relative level (83.4 vs. 77.9%, $p < 0.01$) during the 20-min duration of the session. The average value during high-intensity intervals was 181.5 bpm or 92.3% of the estimated HR_{max}. Regarding lactate released, there were significant TIME × TREATMENT effect between HIIT, MICT, and CTRL ($p < 0.01$) at both 3 min post-exercise [Δ (mean ± SD): 9.32 ± 4.04 vs. 0.79 ± 1.01 vs. 0.014 ± 0.39 mmol/L, respectively] and 15 min post-exercise [Δ (mean ± SD): 7.31 ± 3.17 vs. 0.41 ± 0.67 vs. 0.019 ± 0.38 mmol/L, respectively] measures.

Stroop reaction time

Once the adequate manipulation of the Stroop Test at the two time-points of measurement was confirmed (for further details, see "Stroop test check" in the method section), an ANOVA RM 2 (TIME: Pre-Post) × 3 (TREATMENT: HIIT, MICT, CTRL) was carried out to analyze possible differences in the reaction times for each condition of the Stroop test (congruent, neutral and incongruent).

Congruent condition

There was a significant main effect of TIME [$F_{(1, 35)} = 55.69$, $p < 0.001$, $\eta_p^2 = 0.61$] while no main effect of TREATMENT ($p = 0.28$) was detected. Regarding

TIME × TREATMENT interaction effect for the congruent condition [$F_{(2, 70)} = 20.14$, $p < 0.001$, $\eta_p^2 = 0.37$]. Bonferroni *post hoc* analysis has revealed that both MICT [$t_{(35)} = 4.10$, $p < 0.01$, $d = 0.68$] and HIIT [$t_{(35)} = 9.46$, $p < 0.001$, $d = 1.58$], led to the reduction of the reaction times from the Pre to Post, something that did not occur after the CTRL situation ($p > 0.05$). However, when comparing the Post-session values, we could only find differences between HIIT and CTRL [$t_{(35)} = 4.35$, $p < 0.001$, $d = 0.73$], determined by the effect size of the improvement. Therefore, the effect size of the improvement following the MICT was insufficient to differentiate the Post-response between the MICT session and the CTRL situation (Figure 1A).

Neutral condition

There was a significant main effect of TIME [$F_{(1, 35)} = 16.13$, $p < 0.001$, $\eta_p^2 = 0.31$] while no main effect of TREATMENT ($p = 0.67$) was detected. We have also observed a TIME × TREATMENT interaction effect for the neutral condition [$F_{(2, 70)} = 4.99$, $p < 0.01$, $\eta_p^2 = 0.13$]. Bonferroni *post hoc* analysis has demonstrated Pre-Post differences only for the HIIT session [$t_{(35)} = 5.01$, $p < 0.001$, $d = 0.84$] (Figure 1B).

Incongruent condition

There was a significant main effect of TIME [$F_{(1, 35)} = 19.11$, $p < 0.001$, $\eta_p^2 = 0.36$] while no main effect of TREATMENT ($p = 0.15$) was detected. Finally, we have also ascertained a TIME × TREATMENT interaction effect for the incongruent condition [$F_{(2, 68)} = 8.07$, $p < 0.001$, $\eta_p^2 = 0.19$].

Bonferroni *post hoc* analysis has revealed a Pre-Post effect only for the HIIT session [$t_{(34)} = 5.53$, $p < 0.001$, $d = 0.93$]. Moreover, after having analyzed Post-session reaction times, we have also observed improvements following HIIT protocol when compared with CTRL [$t_{(34)} = 3.91$, $p < 0.01$, $d = 0.66$] (Figure 1C).

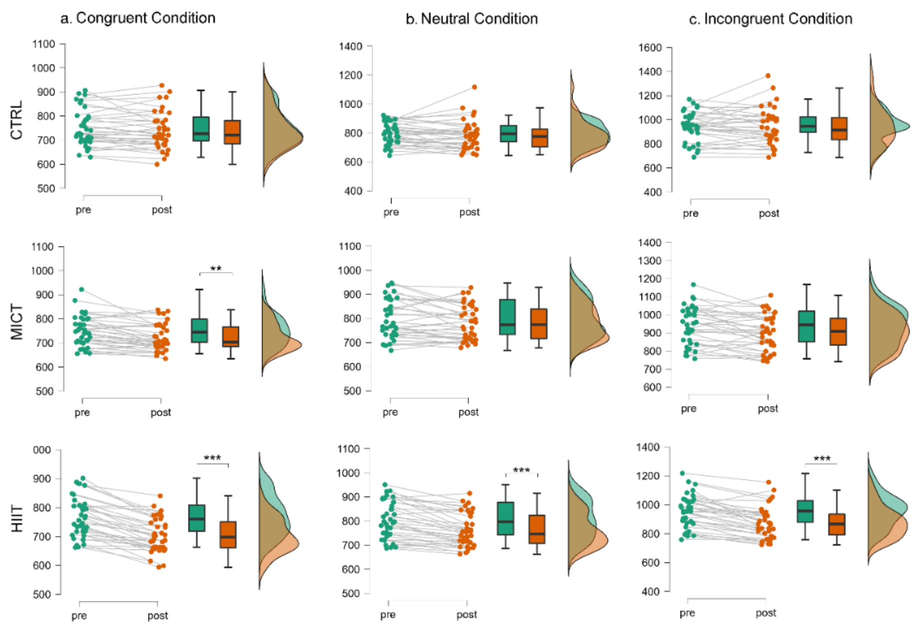

Figure 1. Raincloud plots for time in ms on the three conditions of the Stroop Reaction Time ANOVA RM. Significant effect of time *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. **(A)** Congruent Condition of the Stroop Test. **(B)** Neutral Condition of the Stroop Test. **(C)** Incongruent Condition of the Stroop Test.

Wellbeing

Subjective vitality

With regards to subjective vitality, a TIME × TREATMENT interaction effect was observed [$F_{(1.57, 53.53)} = 4.70$, $p = 0.02$, $\eta_p^2 = 0.12$] since the opposite trend existed between the exercise protocols (with the tendency to improve) vs. the CTRL situation (with the tendency to get worse). However, the Bonferroni *post hoc* analysis found no statistically significant differences.

Thus, the between-group differences found in ANOVA are the consequence of the distinct evolution of the variables (Figure 2A).

Affective state

A TIME × TREATMENT interaction effect was found for the positive Affective state, [$F_{(1.57,\ 53.35)} = 4.65$, $p = 0.02$, $\eta_p^2 = 0.12$], where the tendency to get worse was true for both HIIT and CTRL, but the opposite trend (the tendency to increase) was revealed for MICT. Nonetheless, the Bonferroni *post hoc* analysis did not find any statistically significant differences. This would suggest that differences observed in the ANOVA RM are concerned with the different trends of the variables and not with the significant changes following interventions (Figure 2B).

Regarding negative affective state, there was no interaction effect between Time and Treatment [$F_{(2, 68)} = 2.45$, $p = 0.09$, $\eta_p^2 = 0.06$] (Figure 2C).

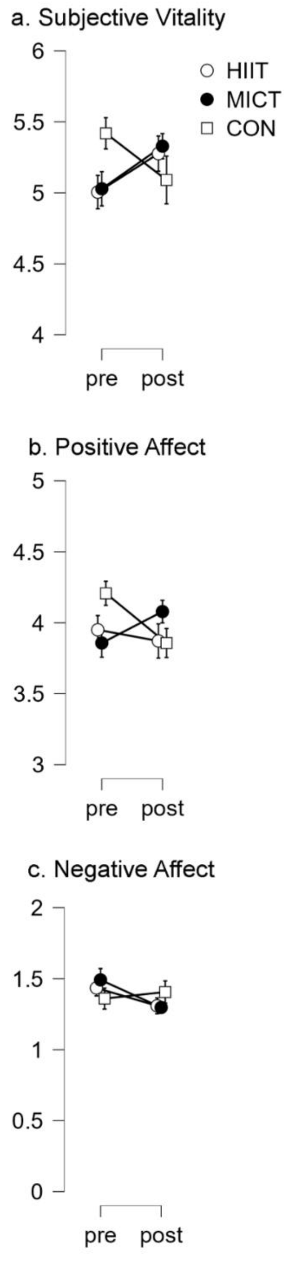

Figure 2. Wellbeing results in pre and post-treatment. Results represent the scale value in the wellbeing questionnaires. **(A)** Subjective vitality results. **(B)** Positive affect results. **(C)** Negative affect results.

Interaction of cognitive response with BDNF polymorphism

Genetic analysis has revealed 11 subjects with the val/val coding, 14 with the val/met coding and 11 with the met/met coding.

No between-subject effects were found for any of the included variables based on the BDNF val66met gene factor ($p > 0.05$). The ANOVAs RM 2 × 3 × 3 (TIME × TREATMENT × BDNF val66met) were non-significant in all Stroop conditions: congruent condition [$F_{(4, 66)} = 0.66$, $p = 0.62$, $\eta_p^2 = 0.04$], neutral condition [$F_{(4,66)} = 0.47$, $p = 0.75$, $\eta_p^2 = 0.03$] nor incongruent condition [$F_{(4, 66)} = 0.66$, $p = 0.62$, $\eta_p^2 = 0.04$].

Correlation analysis

Correlations were identified between changes (Δ) in LA concentration during the cognitive task (at 15 min post-exercise) and Δ in reaction times in congruent condition ($r = -0.49$, $p < 0.001$; Figure 3A), neutral condition ($r = -0.18$, $p = 0.07$; Figure 3B), and incongruent condition ($r = -0.28$, $p < 0.01$; Figure 3C). The analysis of correlations between lactate release at the 15-min post-exercise mark and faster response time in Stroop test conditions separately for each experimental protocol (CTRL, MICT, and HIIT) revealed a correlation between lactate levels and cognitive improvement in congruent test condition following HIIT protocol ($r = -0.366$, $p = 0.028$). This observation did not hold true for any other test condition-protocol pairing ($p > 0.05$ in all of them).

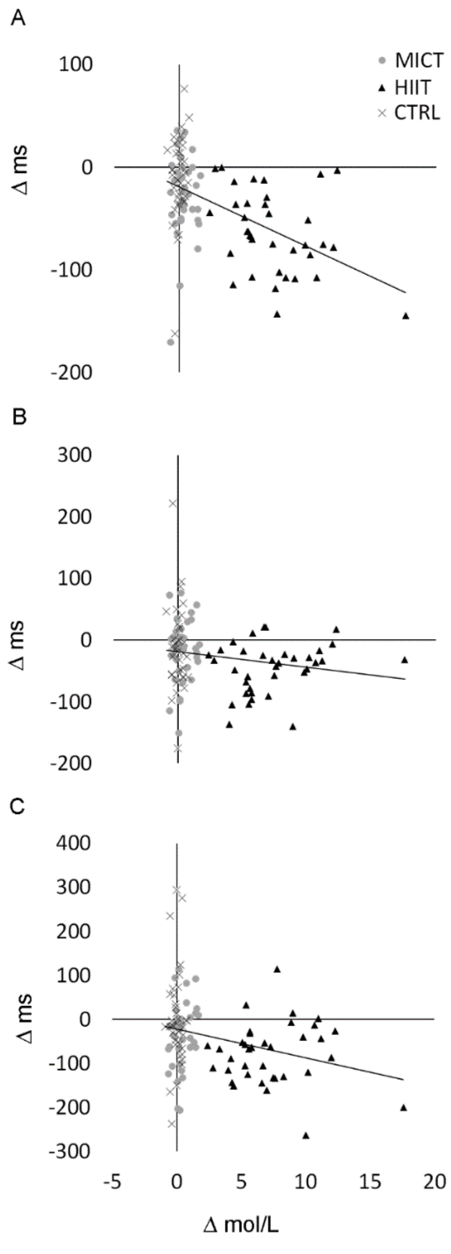

Figure 3. Correlation between lactate increases and improvements in the different conditions of the Stroop test. r and p of the correlations can be shown in text. **(A)** Congruent condition. **(B)** Neutral condition. **(C)** Incongruent condition.

We have also found correlations between changes (Δ) in psychological wellbeing (subjective vitality) and reaction times (Congruent condition; $r = -0.22$, $p = 0.02$), which means the higher is the vitality, the faster is the response.

DISCUSSION

Our main findings suggest that HIIT elicited superior benefits on processing speed and inhibitory control, both assessed employing the Stroop test. This discovery highlights the crucial role of exercise intensity in producing a cognitive response in young college students. Moreover, we have found a positive association between lactate released from the exercising muscle and cognitive improvements. This association could imply that lactate is one of the mechanisms underlying cognitive gains following acute physical exercise. Regarding wellbeing, a positive trend was observed after both exercise protocols (HIIT and MICT) versus CTRL, without differences between both exercise conditions. Lastly, a genetic marker, BDNF val66met did not determine cognitive response to exercise in young college students.

In the present study, improvements in all three Stroop conditions were only evident after a HIIT session when the cognitive task was administered 15 min after the cessation of exercise. These results agree with the observations of Chang et al. (2012), who showed more pronounced improvements following higher exercise intensities and better results after 15 min. This observation could give us a better understanding of the impact of physical exercise on distinct cognitive domains. On one side, higher performance under congruent and neutral conditions indicates improved basic processing speed (Chang et al., 2019). Nonetheless, we have also observed a positive effect on inhibitory control (i.e., incongruent condition; Chang et al., 2019). In terms of the manipulation of the Stroop task, our data has demonstrated longer reaction times and worse precision index in the incongruent condition than in any of the two remaining stages (congruent and neutral). These latter observations are typically associated with the so-called Stroop effect (Mac Leod, 1991; Milham et al., 2002; Chang et al., 2019). It is also worth noting that we have not found any differences in precision between the experimental protocols (HIIT, MICT, and CTRL). The said finding, combined with the previously mentioned differences between cognitive task conditions, suggests that our manipulation of the Stroop test was adequate, and the positive changes following exercise bout were due to faster responses and not as a result of the compensatory response between speed and precision (Chang et al., 2019).

These results agree with the previously reported effects of exercise on both processing speed and inhibitory control in older (Chu et al., 2015) and young and middle-aged subjects (Chu et al., 2017; Chang et al., 2019). However, traditionally, studies chose to explore the impact of moderate-intensity aerobic exercise and rarely compared this training protocol to distinct modalities (Leahy et al., 2020). There is also a lack of data available on the dose–response relationship and the implications this relationship could have on biological markers and cognitive function (Herold et al., 2019). Nevertheless, there is some evidence in the sample of similar characteristics to ours that between two continuous exercise protocols (moderate and high intensity), moderate-intensity exercise led to an acute improvement of executive function (Loprinzi and Kane, 2015). However, in a more recent work, the same authors have observed an improved memory function after a high-intensity bout, yet again in young college students (Loprinzi et al., 2021). A recent meta-analysis exploring the acute effects of high-intensity exercise (any high-intensity exercise, not limited to HIIT protocols) on executive function has established significant effects of exercise compared to non-exercise control (Moreau and Chou, 2019). This effect was diminished when comparisons were made against other exercising groups, including protocols of light and moderate efforts (Moreau and Chou, 2019). Nonetheless, when focusing on comparisons between HIIT and MICT, some studies have demonstrated that HIIT has been shown to elicit health benefits to a larger extent than MICT. Among these are the effects on cardiovascular and metabolic health (Talanian et al., 2007; Hood et al., 2011) and brain health, where improvements in executive function after HIIT are more pronounced compared to MICT (Tsukamoto et al., 2016; Oberste et al., 2019; Mekari et al., 2020).

In recent years, the growing interest in exploring the mechanisms underlying the cognitive response following physical exercise through the physiological lens brought to attention certain metabolites, including lactate, which has been proposed as a regulator of redox status and neuronal activity (Hashimoto et al., 2021). Recent discoveries point to the relationship between lactate and exercise intensity as a viable explanation of the superiority of HIIT against

MICT in triggering a cognitive response (Tsukamoto et al., 2016, 2017; Hashimoto et al., 2018). It is well-known that HIIT generates higher levels of BDNF (Saucedo Marquez et al., 2015), and the latter could be linked to lactate released from the exercising muscle (Ferris et al., 2007). It has been previously reported that lactate could cross the blood–brain barrier (Hashimoto et al., 2018; El Hayek et al., 2019; Nicola and Okun, 2021) and induce BDNF expression in the brain (Müller et al., 2020). In our study, we have observed correlations between lactate release and acute improvement in cognitive response. Interestingly, when we performed a separate analysis for each exercise intensity, we observed the associations between lactate and cognitive improvement in the congruent condition following the HIIT protocol. This improvement in cognitive function, thus, was a consequence of an increased processing speed rather than a better cognitive inhibition. Interestingly, in one of our former studies, we observed how a 10-week High-Intensity Functional Training (HIFT) program induced chronic positive changes in processing speed in young adults (Ballester-Ferrer et al., 2022), similar to the acute effects of exercise in the present study.

In an attempt to associate these acute modifications with the long-term effects of regular practice of physical exercise, it has been reported that baseline BDNF levels were elevated after 3 months of HIFT (Murawska-Cialowicz et al., 2015). These findings make it plausible that chronic changes result from repeated exposure to the acute exercise stimulus and release factors such as BDNF and lactate (Hashimoto et al., 2021). Nonetheless, not all studies have corroborated this relationship. Furthermore, some authors have proposed an inverted U-shaped perspective in the dose–response relationship when reporting the effects of acute exercise (Pontifex et al., 2019). This heterogeneity in the literature could be accounted for by the differences in the selected training modality and exercise protocol, baseline fitness of the participants, the cognitive task employed, or the timing of the cognitive stimuli following exercise (Chang et al., 2012). Concerning exercise protocol, HIIT should not be confused with other types of high-intensity training, some of which did show deleterious effects on cognitive function (Wang et al., 2013; McMorris, 2016). The benefits of interval training (HIIT) are associated precisely with the interval nature of this exercise mode, which aids in lactate liberation, but limits the release of catecholamines and mental stress (Hashimoto et al., 2018). In any case, future research should focus on increasing the evidence through the dose–response relationship perspective in all age groups. Knowledge gained from such studies should help design effective and efficient protocols to improve cognitive function.

Given the putative role of BDNF in cognition, studies exploring the cognitive response to physical exercise should include the Val66Met polymorphism as a moderator variable. The latter could reduce levels of released BDNF and thus, have a direct impact on the cognitive response (Kujach et al., 2019). Along this line of thought, some observational studies have revealed the moderator effect of the Val66Met polymorphism on the exercise-cognition relationship in older adults, along with the benefits associated with the Val/Val SNP (Canivet et al., 2015). However, in our interventional study we could not find significant interactions of the BDNF polymorphism in the exercise-cognition relationship in young college students. This finding agrees with the results reported previously by interventional studies, with the majority revealing the positive effects of exercise on cognition against control conditions, independent of the polymorphism (de Las Heras et al., 2022). Along the same lines, only 31% of interventional studies where the BDNF polymorphism was considered an independent variable reported its moderating effect. Meanwhile, the percentage of observational studies with the same objective was around 82%; however, the results were inconclusive, with the moderating effect of the BDNF polymorphism going in either direction (de Las Heras et al., 2022). The observed differences between the two types of studies could be explained by the presence of distinct mediating factors, such as the participants' age. For instance, observational studies generally selected older subjects compared to younger samples of interventional research (de Las Heras et al., 2022). It has been previously proposed that Val66Met SNP could determine the reduction in brain reserve during the aging process and define distinct cognitive responses in older populations (Lindenberger et al., 2008). If true, this would suggest that the moderating effect of the BDNF polymorphism in the exercise-cognition relationship becomes apparent later in life, supporting the results of our study on college students. Moreover, aside from age and methodological differences, other moderators such as biological sex, gene interactions, and ethnicity could be influencing the disparate findings (de Las Heras et al., 2022). Given all the above, there does not seem to exist consensus in the literature on the role of the BDNF SNP in the exercise-cognition relationship (de Las Heras et al., 2022), and the benefits of exercise on cognition may well be independent of the latter, as we have observed in our study. Future investigations are required to confirm or refute these assumptions to contribute further to exercise-cognition research.

In our study, along with lactate and BDNF polymorphism as possible mediators of the exercise-cognition relationship, we have also explored the mediating role of behavioral and socioemotional factors (Stillman et al., 2016). Although these factors have shown promising effects on cognition, some variables of this type, such as wellbeing, have been less studied in the literature related to cognition (Stillman et al., 2016). Previous research has revealed how moderate-intensity exercise was conducive to psychological wellbeing; meanwhile, high-intensity exercise could lead to feelings of displeasure (Ekkekakis, 2003). However, some studies have demonstrated a rebound effect, where although at the start of high-intensity effort, the perception of wellbeing was reduced, following a period of approximately 20 min after the exercise cessation, an improvement in wellbeing score was observed (Jung et al., 2014; Malik et al., 2019). In this regard, in our study, psychological variables were assessed some time after the exercise session, and we have observed that psychological variables included in the analysis were modified differently in response to experimental treatments. For instance, a positive trend was observed after both exercise protocols (HIIT and MICT) for subjective vitality; meanwhile, the control situation without exercise revealed a negative trend. In terms of positive affect, negative changes were observed after HIIT and CTRL. However, an increase in positive affect followed MICT. For the negative affect, we could not find any significant changes between experimental conditions. Along the same lines, and in agreement with the results reported by Cervelló et al. (2014), alterations in psychological wellbeing were distinct between experimental conditions, with a positive trend observed after MICT but not after CTRL, where a negative trend was discovered. Concerning HIIT, we could not detect any significant differences between HIIT and MICT in the psychological variables examined. This would imply that exercise intensity had no impact on the psychoemotional state of young college students following exercise. This latter finding somewhat agrees with the previously reported results (Cervelló et al., 2014). Especially when it comes to HIIT, the importance of exercise intensity in influencing psychological state is not clear. For instance, a recent meta-analysis exploring the effects of HIIT on cognitive function and psychological wellbeing has observed a positive trend for both variables after HIIT; however, the effect size was greater for cognitive improvements than for wellbeing (Leahy et al., 2020).

In an attempt to clarify the relationship between cognitive function and psychological wellbeingwe should also point to a negative correlation between changes in processing speed (a congruent condition in the Stroop task) and subjective vitality, suggesting an association exists between improvements in psychological wellbeing and cognitive function (lower reaction times). If true, psychological wellbeing could be a behavioral and socioemotional mediator of cognitive response following exercise (Stillman et al., 2016). We, thus, propose the relevance of evaluating psychological wellbeing in response to exercise, where it could modulate learning and cognitive function (Garcia et al., 2015; Yu et al., 2017). Additionally, from a practical standpoint, taking wellbeing into account could help ensure high adherence rates, especially relevant in clinical populations (Salman et al., 2019). The intrinsic benefit derived from optimal wellbeing is important in and on itself and has placed psychological wellbeing on the list of priorities of the European Union (Miret et al., 2015).

Finally, a few positive aspects of our study should be mentioned. A recent meta-analysis failed to perform a moderator analysis between HIIT and MICT due to the lack of studies comparing the two modalities (Leahy et al., 2020), a limitation that has been addressed in our work. Although some studies have considered younger populations in their samples (Ishihara et al., 2021), in general, recent publications have highlighted the need to conduct rigorous research in understudied groups, including children under 5, adolescents, and young adults (Stillman et al., 2020). To date, a vast majority of published work which attempted to explore the relationship between physical exercise and cognitive function was applied in older adults (Stillman et al., 2020). Nonetheless, according to a recent meta-analysis, most studies exploring the acute effects of high-intensity exercise on executive function included adults aged 19–30 in their samples (Moreau and Chou, 2019).

Limitations

The present study has some limitations which are worth mentioning. The volume of the exercise sessions in the study was standardized to 20 min based on the previous evidence where this exercise duration was associated with optimal cognitive gains (Chang et al., 2019; Oberste et al., 2019). Conversely, we modified the exercise intensity. Nonetheless, the combination of distinct volumes and intensities could provide insight into the optimum interaction between the two. Our study still revealed superior benefits of HIIT on processing speed and inhibitory control; both evaluated through the Stroop test. These findings have allowed us to infer that HIIT positively impacted executive control (Chang et al., 2019). However, it should be mentioned that executive function is comprised of multiple subdomains, of which some could manifest a unique response to exercise. Thus, future investigations should include different subdomains of executive function in their analysis. At the same time, and guided by previous research (Hashimoto et al., 2018; El Hayek et al., 2019; Nicola and Okun, 2021) we have hypothesized that elevated blood lactate during high-intensity exercise could explain cognitive gains following this exercise mode. In this sense, while we did observe significant associations between lactate concentrations and cognitive improvements, we have only measured blood lactate and inferred that brain lactate levels have also increased in response to exercise. Thus, we could not establish a cause-and-effect relationship and hope that, based on our theoretical assumptions, future studies would attempt to perform additional experiments. We should also highlight the limitation of our sample size concerning the genetic analysis. Given the complexity of ANOVA RM performed (2 × 3 × 3, Time × Treatment SNP), we should have incorporated a sample of 111 individuals to conserve the study power of 0.8, which was out of reach, given our possibilities. Larger samples are required for analysis of similar complexity to ensure the validity of the statistical data.

CONCLUSION

Our study demonstrated how exercise could be a helpful tool to improve inhibitory control. Moreover, the effect size of an acute bout of HIIT was larger than that of MICT. As a plausible mechanism underlying these results, lactate released during HIIT was associated with cognitive improvements, ultimately leading us to conclude that exercise above the lactate threshold derives the most benefits for cognition in college students. Moreover, psychological wellbeing, which was positively affected in both experimental conditions (more so in MICT than in HIIT) but not in CTRL, could be related to cognitive gains observed after exercise. As such, our analysis has revealed a link between increased subjective vitality (one of the subdimensions of psychological wellbeing) and improved executive function. These observations highlight the importance of considering multiple mediators of the exercise-cognition relationship.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Oficina de Investigación Responsable de la Universidad Miguel Hernández de Elche. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB-F, BB-L, EC, and DP contributed to conception and design of the study and wrote the sections of the manuscript. JB-F, AR, and BB-L organized the database. JB-F, AR, and DP performed the statistical analysis. JB-F and DP wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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CONFLICT OF INTEREST

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.

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ANEXO 3

ESTUDIO AGUDO 2

Memory Modulation by Exercise in Young Adults Is Related to Lactate and Not Affected by Sex or BDNF Polymorphism.

Nota. Este estudio se encuentra publicado.

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8.3. Anexo 3

8.3.1. Estudio agudo 2. Memory Modulation by Exercise in Young Adults Is Related to Lactate and Not Affected by Sex or BDNF Polymorphism.

Abstract

Currently, high-intensity interval exercise (HIIE) is on the rise compared to moderate-intensity exercise (MIE) due to its similar benefits for health and performance with low time requirements. Recent studies show how physical exercise can also influence cognitive function, although the optimal dose and underlying mechanisms remain unknown. Therefore, in our study, we have compared the effects on visuospatial and declarative memory of different exercise intensities (HIIE vs. MIE), including possible implicated factors such as lactate released after each session and the Brain-Derived Neurotrophic Factor (BDNF) genotype. Thirty-six undergraduate students participated in this study. The HIIE session consisted of a 3 min warm-up, four 2 min sets at 90–95% of the maximal aerobic speed (MAS) with 2 min of passive recovery between sets, and a 3 min cooldown, and the MIE session implies the same total duration of continuous exercise at 60% of the MAS. Better improvements were found after HIIE than MIE on the backward condition of the visuospatial memory test ($p = 0.014$, $\eta_p^2 = 0.17$) and the 48 h retention of the declarative memory test ($p = 0.04$; d = 0.34). No differences were observed in the forward condition of the visuospatial memory test and the 7-day retention of the declarative memory test ($p > 0.05$). Moreover, non-modifiable parameters such as biological sex and BDNF polymorphism (Val/Val, Val/Met, or Met/Met) did not modulate the cognitive response to exercise. Curiously, the correlational analysis showed associations ($p < 0.05$) between changes in memory (visuospatial and declarative) and lactate release. In this sense, our results suggest an important role for intensity in improving cognitive function with exercise, regardless of genetic factors such as biological sex or BDNF Val66Met polymorphism.

Keywords: *cognitive function, BDNF, physical exercise, intensity, blood lactate*

INTRODUCTION

Evidence suggests that the practice of physical exercise has positive effects on cognitive function, with benefits attributed to both acute(Chang, Labban, Gapin, & Etnier, 2012; Herold, Törpel, Schega, & Müller, 2019; Oberste et al., 2019; Pontifex et al., 2019; Soga, Masaki, Gerber, & Ludyga, 2018; Stillman, Cohen, Lehman, & Erickson, 2016; Stillman, Esteban-Cornejo, Brown, Bender, & Erickson, 2020) and chronic exercise (Herold, Törpel, et al., 2019; Landrigan, Bell, Crowe, Clay, & Mirman, 2020; Ludyga, Gerber, Pühse, Looser, & Kamijo, 2020; Soga et al., 2018; Stillman et al., 2016; Stillman et al., 2020). However, there is high variability in the observed effect sizes (Roig, Nordbrandt, Geertsen, & Nielsen, 2013), which may be explained by the distinct characteristics of the physical exercise design, such as the type or dose, the cognitive domain assessed, or individual differences, such as the genotype (de Las Heras et al., 2022). Moreover, most studies on the relationship between exercise and cognitive function were conducted in children or older adults; meanwhile, adolescent and young adult populations remain underrepresented (Stillman et al., 2020). Therefore, although a large body of literature has focused on the study of the relationship between exercise and cognition, there is no clear agreement on the optimum dose of exercise and the associated mechanisms to produce greater improvements in cognitive function and even less so in young adults. The influence of common mediator variables, such as sex or genetic profile, on the aforementioned relationship also remains largely unresolved.

In an attempt to optimize current guidelines for exercise prescription to improve cognition, research has focused on the role of exercise dose in modulating the changes in cognitive function (Chang et al., 2012; Herold, Müller, Gronwald, & Müller, 2019; Ludyga et al., 2020; Oberste et al., 2019). Insights gained from such research could explain the previously observed heterogeneity in response and reveal the underlying mechanisms. In their meta-analysis, Chang et al. (2012) observed how, whenever there is sufficient rest after an exercise bout, very high-intensity (>93% Heart Rate) exercise would produce the greatest benefits in cognitive function. Along the same lines, a more recent review article (Oberste et al., 2019) corroborated these observations concerning the intensity of the exercise, with high-intensity interval exercise (HIIE) accounting for greater improvements in inhibitory control, followed by vigorous-intensity and moderate-intensity continuous exercise (MIE). In agreement with these conclusions, it has been revealed that lower volume sessions (which, in turn, allow to sustain higher intensities) are associated with a better response, with sessions below twenty minutes, in particular, leading to superior effects (Chang et al., 2019; Oberste et al., 2019). Interestingly, following the dose–response perspective, recent studies have suggested that lactate released during high-intensity exercise may play an important role in acute cognitive enhancement in response to exercise (Hashimoto, Tsukamoto, Ando, & Ogoh, 2021). Recent observations in mice have revealed how lactate released from exercising muscles during high-intensity bouts can cross the blood–brain barrier and induce BDNF expression in the hippocampus, improving learning and spatial memory (El Hayek et al., 2019). Siebenmann et al. (2021) proposed that the same mechanisms may hold true for humans. Lactate release has been previously correlated with cognitive performance in humans (Hashimoto et al., 2021). Moreover, as El Hayek et al. (2019) have demonstrated, lactate enhanced BDNF production in the hippocampus, and BDNF, in turn, has been associated with hippocampus learning (An, Li, Tang, Xu, & Sun, 2018) and general memory processing (Bekinschtein, Cammarota, & Medina, 2014).

Precisely, the arterio-jugular venous lactate difference was measured during incremental cycling exercise until exhaustion, concluding that brain lactate uptake during exercise was directly determined by the increase in arterial lactate concentration, with the latter rising in proportion to intensity. Moreover, lactate released during exercise could exert positive effects on brain health, modulating molecular pathways related to neurogenesis (Morland et al., 2017) and promoting neuronal survival (Lev-Vachnish et al., 2019).

The duration of the effects of exercise on cognition is another relevant topic in the literature (Loprinzi, Roig, Etnier, Tomporowski, & Voss, 2021; Roig et al., 2016). In this sense, exercise could be linked to distinct phases of declarative memory. Thus, the effects of exercise have been evaluated, depending on the time point of application, in the acquisition (encoding and consolidation), storage, and retrieval stages (Loprinzi et al., 2021). It has been proposed that to isolate the effects of acute exercise on mechanisms related to memory consolidation, the exercise session should be performed after encoding, during the consolidation window, and not too close to the memory retrieval stage (Loprinzi et al., 2021). Addressing the memory consolidation phase has proven to be the most beneficial strategy for memory enhancement through exercise (Roig et al., 2016). In this regard, exercise could transiently alter the availability of catecholamines (norepinephrine and dopamine) and neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) (Skriver et al., 2014) during consolidation, which could lead to an improvement in long-term memory.

Related to the secretion of BDNF, it is known that is regulated by the homonymous gene, which has a single nucleotide polymorphism (SNP) called SNP rs6262 or BDNF Val66Met gene polymorphism. This polymorphism substitutes a valine (Val) for methionine (Met) at codon 66. Individuals may present with either two valine SNPs (Val/Val), one valine and one methionine (Val/Met), or two methionines (Met/Met). The polymorphism exhibited by methionine (Met/Met) reduces BDNF secretion (Egan et al., 2003) and could explain the observed diminished response to exercise in terms of its effects on declarative memory in Met/Met carriers (Canivet et al., 2015). These findings allow us to infer the possible mediator role of the genomic profile and, in particular, the presence of BDNF Met/Met polymorphism on the effects of exercise on learning on the level of an individual.

In addition to the BDNF polymorphism, other aspects have been included in studies on exercise and cognition as possible moderators of the cognitive response. In this sense, biological sex is considered a powerful moderator (Barha, Hsu, Ten Brinke, & Liu-Ambrose, 2019; Barha & Liu-Ambrose, 2020; Ludyga et al., 2020). BDNF release differs between sexes, but the impact and mechanisms of such differences remain unexplored (Wei, Wang, & Xu, 2017). At a physiological level, men should be able to release more BDNF after acute exercise (Szuhany, Bugatti, & Otto, 2015). Moreover, the BDNF genotype does not translate into cognitive benefits in females, but the opposite response has been reported in male subjects (Watts, Andrews, & Anstey, 2018). However, there is controversy when observing the cognitive response, with some studies reporting a better response to aerobic exercise in women (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017; Colcombe & Kramer, 2003) while others have reported worse outcomes in those studies with a higher percentage of female subjects (Ludyga et al., 2020). Thus, ideally, studies should consider the inclusion of both sexes in their samples to increase the evidence in this regard.

In an effort to make up for the aforestated gaps in the literature and expand our knowledge of the mechanisms behind cognitive enhancement following physical exercise, we hypothesized the following: (i) HIIE would elicit better responses in short-term visuospatial memory and long-term formal memory consolidation than MIE, (ii) lactate release would be positively associated with cognitive improvements, (iii) subjects with the presence of at least one Met allele would score lower in memory tasks, and (iv) following exercise, the cognitive response in women would be amplified when compared to men.

MATERIALS AND METHODS

Participants

Thirty-six undergraduate students (mean ± SD, age: 22.25 ± 2.94, height: 1.69 ± 0.09, weight: 70.03 ± 11.29, Body Mass Index (BMI): 24.25 ± 2.56, %fat mass: 22.73 ± 6.93, maximal aerobic speed (MAS): 14.82 ± 1.10, Maximum Heart Rate ($HR_{max)}$: 196.22 ± 8.22) participated in this study. Prior to the study, all participants filled out the "Physical Activity Readiness Questionnaire" (PAR-Q) and signed written informed consent clarifying a range of measurements and exercise sessions contemplated within the study protocol and the anonymity and confidentiality of the extracted data. The experimental design was thought out according to the most recent revision of the Declaration of Helsinki and was approved by the Ethics Committee of the University (UMH.CID.DPC.02.17). The participants were advised to avoid strenuous physical exercise 24 h prior to every protocolled exercise session. In total, three sessions, separated by a week, were carried out, with each session scheduled for 9 a.m. Caffeine use before the exercise was discouraged. Water intake was restricted to 30 min prior to the visit to the laboratory, as indicated by the manufacturer of the saliva tests.

The sample size was calculated using G-power, where alpha was 0.05, and power was 0.8. We were looking for at least a medium effect size ($0.01 < \eta_p^2 < 0.06$). The dependent variable was TIME in the ANOVA RM TIME vs. Condition. With $\eta_p^2 = 0.05$ assumed for all the variables, the sample calculation for a priori ANOVA RM 2×2 was of 34 participants. In a post hoc analysis, the ANOVA RM showed a η_p^2 of 0.16 and 0.17, which means that the power of our study is 0.99.

Experimental Procedure

Participants attended the laboratory on three separate occasions. The first visit included the filling in of pre-participation questionnaires and informed consent by the participants, the collection of saliva samples to establish BDNF polymorphism, and a graded exercise test to determine the workload corresponding to the HIIE and MIE. The following two visits to the laboratory were randomized and counterbalanced to carry out the experimental conditions (HIIE or MIE) (Figure 1). For both visits, the participants were required to be present in the laboratory at 9 a.m.

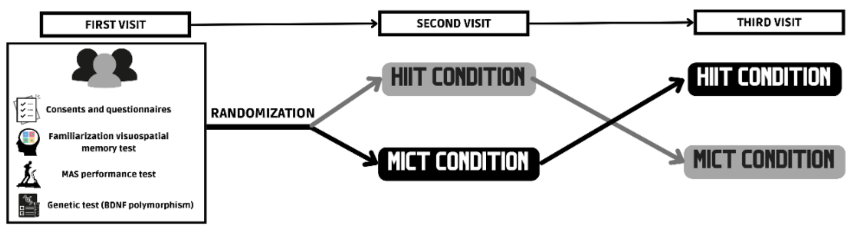

Figure 1. *Study design*

The Visuospatial Memory was assessed before and after each experimental condition. The post-measurement was administered 15 min after the cessation of the exercise. Previous research has identified this time frame as optimal for maximizing the cognitive response to exercise (Chang et al., 2012; Oberste et al., 2019). The Long-Term Formal memory task was performed before each of the experimental conditions (the phase of encoding), thus placing the exercise session itself during the consolidation stage (Loprinzi et al., 2021).

Blood lactate samples were drawn prior to exercise and 3 and 15 min upon cessation of the main exercise, coinciding with the end of the exercise protocol and marking the start of the post-measurements of the cognitive tasks.

The experimental protocol is summarized in Figure 2.

Figure 2. Experimental protocol design.

Experimental Conditions

The experimental conditions (HIIE and MIE) were carried out on a treadmill in randomized and counterbalanced order (Figure 1). The sessions were performed one week apart. Both sessions included a 3 min warm-up at 60% MAS. In the case of MIE, this intensity was sustained for the whole duration of the exercise (20 min). The HIIE session consisted of four bouts of 2 min at 90–95% MAS, interspersed with 2 min of passive recovery, and followed by a 3 min cooldown at walking speed to reach a total of 20 min. The volume of both sessions was, thus, standardized. The decision to limit the duration of both sessions to 20 min was founded in the previous research, where a trend towards better cognitive outcomes, in particular, in executive function, was observed in those sessions with similar volumes (Chang et al., 2019; Oberste et al., 2019). Heart rate

(HR) was monitored using polar H7 chest straps and the Polar Beat app (Polar Electro Oy, Kempele, Finland) (Figure 3).

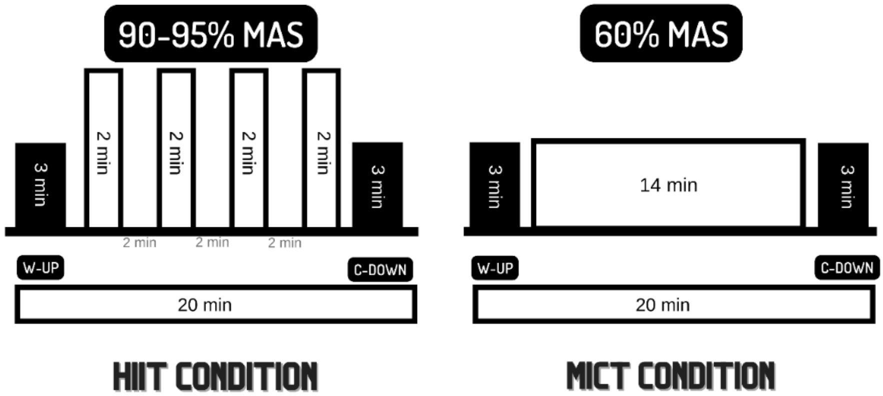

Figure 3. Exercise session design.

Measurements

Graded Exercise Testing

A graded exercise test to volitional exhaustion was conducted on a treadmill to determine the MAS and the maximum HR. An HR measurement was monitored using the polar chest strap H7 (Polar Electro Oy, Kempele, Finland). After a 3 min warm-up at 5 km/h, the speed was increased by 1 km/h every minute until exhaustion. The treadmill was set at a gradient of 1% for both the warm-up and the main part. The participants were not allowed to drink or talk during the test and were asked to refrain from intense exercise for 24 h prior to the testing.

Lactate Blood Sample

To determine the lactate concentrations, blood samples were obtained from the earlobes of the subjects at the beginning of the experimental session and 3 and 15 min after each of the main exercises in the experimental conditions using a portable lactate analyzer (Lactate Scout, SensLab GmbH, Leipzig, Germany).

Genotipe Analysis

Saliva samples were collected with an OrageneTM DNA Saliva Collection Kit (DNA Genotek S.L., Ottawa, ON, Canada). The DNA extraction protocol was provided by the manufacturer. The sample was further analyzed using a quantitative real-time StepOne PCR of the Applied Biosystem (Thermo Fisher Scientific S.A., Waltham, MA, USA), following the protocol of Sánchez-Romero, Dorado, Guarino, and Llerena (2009).

Cognitive Function

Short-Term Visuospatial Memory Task

A digital version of the Corsi Block-Tapping task, widely used to assess visuospatial and short-term working memory (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000) was used. The protocol described by Kessels et al. (2000) contemplates two modalities (Forward and Backward) within the same task. Nine items are visible on the screen, and for each trial, these items are “lit” one by one, at a rate of one item per second, in a randomized order. The first modality (Forward) requires that the participants tap on the items in the same order as they first appeared on the screen, immediately after the last item of the sequence has been displayed. For the second modality (Backward), on the other hand, the participants are instructed to repeat the sequence in reverse order. The participants receive two trials for every sequence with the same number of items. If at least one of the attempts is successful, the next sequence of a greater length is administered. The test is over once the participant fails to replicate two consecutive sequences of the same length. Given the test characteristics, two scoring alternatives can be obtained: on the one hand, the number of successful trials achieved until the end of the test, and on the other hand, the block span (which is equal to the length of the last sequence) for each of the test modalities. The product of both scores gives rise to the total score, which has been shown to be the most reliable variable for assessing changes in this visuospatial memory test (Kessels et al., 2000). Therefore, the test evaluates the following four variables: (i) block span forward (CSF), (ii) total score forward (TSF), (iii) block span backward (CSB), and (iv) total score backward (TSB). In this sense, at the baseline, we observed scores very similar to those reported by Kessels et al. (2000) in healthy individuals. On the other hand, the scores were also very similar at the pre-test of both experimental conditions for both the forward ($p = 0.75$) and backward ($p = 0.91$) modalities.

Long-Term Formal Memory Task

For the formal memory task, the subjects were required to memorize a 15-line text (221 words) with factual information (Izquierdo et al., 2008) about the 1954 Soccer World Cup or the 1967 Handball World Championship. The participants were given 10 min before each experimental situation (MIE and HIIE sessions), thus placing the latter after memory encoding. Memory recall, in turn, was tested following (Loprinzi et al., 2021) 48 h and seven days using a list of questions on ten factual items from either of the two texts (Izquierdo et al., 2008). For each correct answer, the participants were awarded one point. Each one of the two texts was counterbalanced with the experimental condition to eliminate a possible contaminating effect of the text.

Statistical Analysis

The alpha was set to 0.05 for all analyses. The normality of the data set was examined through the Shapiro–Wilk test. Before the main analysis, paired *t*-tests were performed to compare the exercise intensity variables between the MIE and HIIE sessions and to examine possible differences in the pre-assessment of visuospatial memory in both experimental conditions.

To analyze the differences in the visuospatial memory between the experimental conditions, a repeated-measures analysis of variance (ANOVA RM) was performed with two within-subject factors (Time × Condition). Sphericity was computed with Mauchly's sphericity test.

To analyze the differences in long-term memory (recall) on the formal memory test and between the MIE and HIIE intensities, paired *t*-tests or the Wilcoxon signed rank were also calculated according to the data distribution.

Two additional ANOVA RM analyses were conducted separately for BDNF polymorphism (Val/Val, Val/Met, or Met/Met) or sex (male or female) as a between-subject factor to analyze the possible influences of these non-modifiable factors. In the case of finding statistically significant differences in any of the ANOVA RM analyses, post hoc analyses with Bonferroni adjustment were employed.

As a measure of the effect sizes on the ANOVA RM analysis, partial eta-squared (η_p^2) was used. The effect sizes are expressed as partial eta-squared (η_p^2) and are grouped as small (≤0.01), medium (≤0.06), and large (≤0.14) (Cohen, 1992). Finally, Pearson's correlation analyses (r) were used to establish possible associations between the changes (Δ) in blood lactate and cognitive function (Hashimoto et al., 2021).

All the results were analyzed using the JASP 0.16 software (Eric-Jan Wagenmakers, Department of the Psychological Methods University of Amsterdam, Nieuwe Achtergracht 129B, Amsterdam, The Netherlands).

RESULTS

Exercise Characteristics

Both, absolute (164.1 vs. 152.6 bpm, $p < 0.01$) and relative (83.6 vs. 77.8%, $p < 0.01$) HR values were higher in HIIE than MIE for the whole 20 min duration of the session. The average for the HIIE intervals was 181.5 bpm, which corresponded to 92.5% of the HR_{max}, and the average during that same length of time in the MIE session was 155.7 bpm (79% HR_{max}). Regarding the lactate concentrations, significant differences between HIIE and MIE were found at both the 3- (10.18 vs. 1.86 mmol, $p < 0.01$) and 15- (8.17 vs. 1.48 mmol, $p < 0.01$) minutes post-exercise measurements.

Intensity Impact on Memory

Visuospatial memory: The repeated-measures ANOVA revealed the absence of the significant interaction of Time x Condition for CSF [$F_{(1,35)} = 0.97$, $p = 0.33$, $\eta_p^2 = 0.03$] or TSF [$F_{(1,35)} = 0.49$, $p = 0.49$, $\eta_p^2 = 0.014$]. In contrast, there were significant differences for CSB [$F_{(1,34)} = 6.67$, $p = 0.014$, $\eta_p^2 = 0.16$] and TSB [$F_{(1,34)} = 6.79$, $p = 0.014$, $\eta_p^2 = 0.17$]. The post hoc Bonferroni analysis for TSB showed significant differences in pre vs. post HIIE [$t_{(34)} = 2.87$, $p = 0.03$] and post HIIE vs. post MIE [$t_{(34)} = 2.95$, $p = 0.03$] in favor of the HIIE session. In CSB, there was a significant difference in post HIIE vs. post MIE [$t_{(34)} = 2.97$, $p = 0.02$] in favor of the HIIE session (Figure 4).

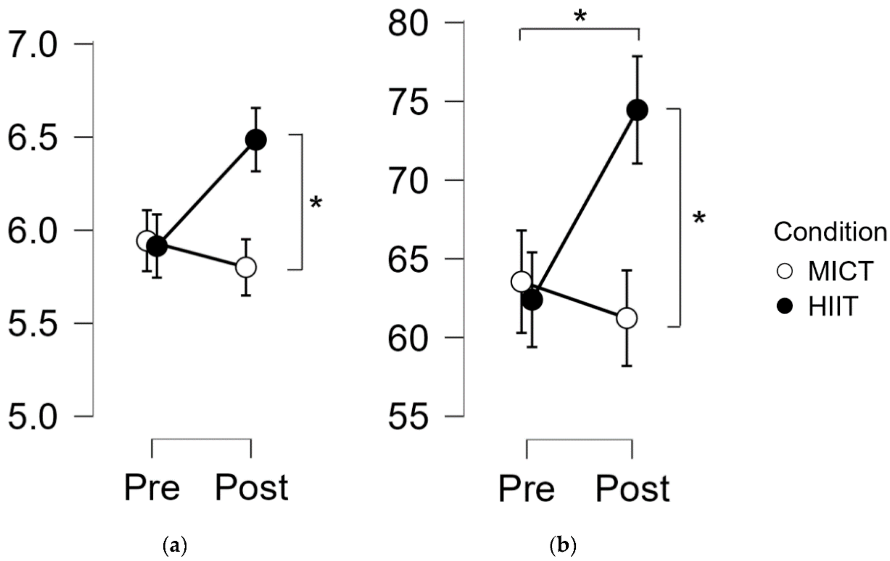

Figure 4. Visuospatial memory results. **(a)** Corsi Span Backward; **(b)** Total Score Backward. *: Indicates a significant effect of time or between conditions ($p < 0.05$).

Formal/Declarative memory test: Paired *t*-tests showed significant differences in the recall of factual information at 48 h in favor of the HIIE session ($p = 0.04$; d = 0.34), which was not the case with recall at 7 days ($p = 0.79$; d = 0.057) (Figure 5).

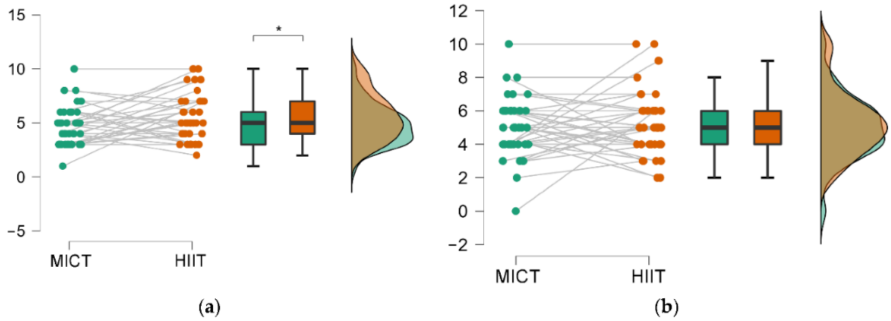

Figure 5. Raincloud plots for the formal memory results. **(a)** Recall at 48 h; **(b)** Recall at 7 days. *: Indicates a significant effect of time or between conditions.

Interaction of Response with Sex and BDNF Polymorphism

To analyze possible differences in the cognitive response dependent on non-modifiable factors, sex and Val66Met were added to the analyses. From the genetic analysis, we found 10 subjects with the Val/Val coding, 15 with the Val/Met coding, and 11 with the Met/Met coding.

No significant differences were found in the Time x Condition x Sex interaction in CSF [$F_{(1,34)} = 1.93$, $p = 0.18$, $\eta_p^2 = 0.054$], CSB [$F_{(1,33)} = 0.09$, $p = 0.77$, $\eta_p^2 = 0.003$], TSF [$F_{(1,34)} = 2.75$, $p = 0.11$, $\eta_p^2 = 0.07$], nor TSB [$F_{(1,33)} = 0.10$, $p = 0.75$, $\eta_p^2 = 0.003$]. No significant differences were found in the Condition x Sex interaction in the FM 48 h recall [$F_{(1,34)} = 1.59$, $p = 0.22$; $\eta_p^2 = 0.04$] nor FM 7 days recall [$F_{(1,34)} = 0.001$, $p = 0.97$; $\eta_p^2 = 0.006$]. No between-subject effects were found for any of the included variables based on the sex factor ($p > 0.05$).

No significant differences were found in the Time × Condition × BDNF Val66Met interaction in CSF [$F_{(2,33)} = 0.69$, $p = 0.51$, $\eta_p^2 = 0.04$], CSB [$F_{(2,32)} = 0.38$, $p = 0.69$, $\eta_p^2 = 0.02$], TSF [$F_{(2,33)} = 1.55$, $p = 0.23$, $\eta_p^2 = 0.08$], nor TSB [$F_{(2,32)} = 0.48$, $p = 0.62$, $\eta_p^2 = 0.03$]. No significant differences were found in the Condition × BDNF Val66Met in any formal memory recall ($p < 0.05$). No between-subject effects were found for any of the included variables based on the BDNF Val66Met gene factor ($p > 0.05$).

Correlation Analysis

Positive correlations were identified between the changes (Δ) in the LA concentration at 3 min (CSB, r = 0.295, $p = 0.013$; TSB, r = 0.363, $p = 0.002$; and Recall 48 h, r = 0.225, $p = 0.058$) and at 15 min (CSB, r = 0.324, $p = 0.006$; TSB, r = 0.428, $p < 0.001$; and Recall 48 h, r = 0.264, $p = 0.025$) (Figure 6).

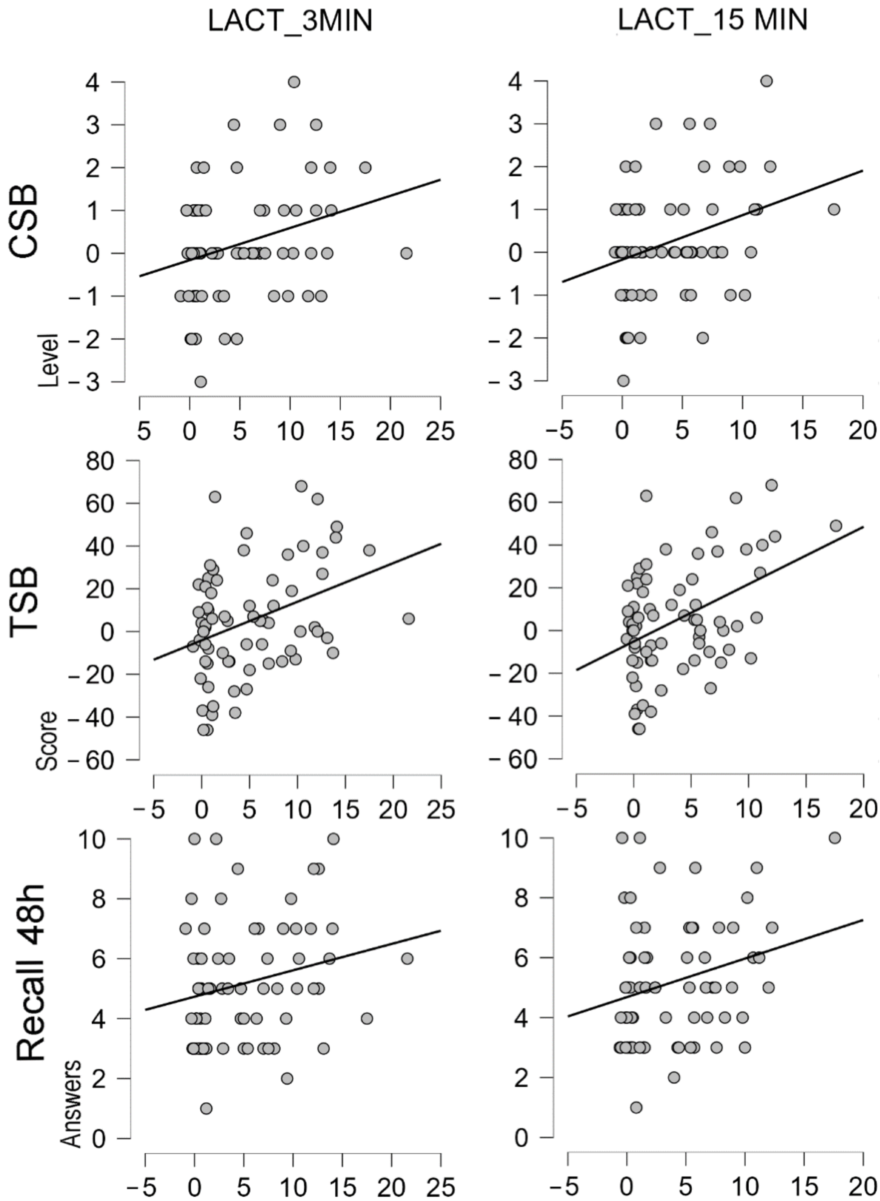

Figure 6. Correlations between changes (Δ) in LA concentration and Δ memory scores. CSB: Corsi Span Backward, TSB: Total Score Backward, Recall 24 h: Formal memory recall at 48 h.

DISCUSSION

Our results indicate an acute performance enhancement in the backward modality of the short-term visuospatial memory task. In this sense, some studies have highlighted the higher complexity of the backward task (Brunetti, Del Gatto, & Delogu, 2014; Vandierendonck, Kemps, Fastame, & Szmalec, 2004). This could be explained by the participation of the distinct working memory subsystems in the two modalities, where the backward condition puts a heavier load on the central executive (e.g., to reverse the sequence) (Brunetti et al., 2014; Vandierendonck et al., 2004). Previous studies exploring the relationship between exercise and memory have generally observed that exercise could have little (Tomporowski & Ellis, 1986) or null (Etnier et al., 1997) impact on the said cognitive domain. However, more recently, the positive effects of acute exercise on both short- and long-term memory were shown (Roig et al., 2013). In this line, Chang et al. (2012) have evaluated the effects of exercise on different types of memory and observed improvements only in free recall and short-term visual memory. In their meta-analysis, they also observed that as long as there is a rest period after the exercise session, the exercise of greater intensity would lead to superior gains in cognitive function, something that we have been able to corroborate with our results. Along the same lines and consistent with our findings, a more recent meta-analysis revealed that the superiority of HIIE concerned executive function, while moderate exercise had only a small effect (Oberste et al., 2019). Therefore, optimizing exercise protocols could be a key element in reducing variability in the cognitive response. As such, current research proposes the exploration of different types or doses of exercise to improve the cognitive response in young adults, with findings similar to ours, where the benefits of HIIE for the executive function are superior compared to MIE (Hashimoto et al., 2018; Tsukamoto et al., 2016; Tsukamoto et al., 2017).

On the other hand, in addition to the acute effects observed in the literature on short-term visuospatial memory (Chang et al., 2012; Roig et al., 2013), it has been suggested that acute physical exercise can benefit long-term declarative memory (Roig et al., 2013). In this sense, we have observed a significant positive effect of exercise intensity on memory recall at 48 h, in favor of the HIIE session, in the long-term formal memory task (Izquierdo et al., 2008). Furthermore, we have placed the exercise session before the memory encoding stage with the intention of testing the impact of exercise intensity on mechanisms related to memory consolidation (Loprinzi et al., 2021). This particular phase of memory processing has been reported to be affected by exercise through the production of neurotrophins and growth factors (Loprinzi et al., 2021). Thus, it has been revealed how exercise plays a central role in altering mediators such as BDNF and hippocampal cell proliferation, with the latter two affecting the exercise–memory relationship (Marin Bosch et al., 2021). Our results suggest that the HIIE session during the consolidation phase favors information recall at 48 h compared to the MIE session. In this sense, and relating it to the mechanisms mentioned above, Saucedo Marquez, Vanaudenaerde, Troosters, and Wenderoth (2015) observed that HIIE was a more powerful stimulus to increase the systemic release of BDNF compared to MIE. The same study also established that a greater synthesis of BDNF in the brain could explain the increased systemic levels of this neurotrophic factor and account for the observed favorable effects of HIIE versus MIE in our study.

Related to the mechanisms underlying the positive effect of HIIE over MIE on memory mentioned above, it is worth clarifying that HIIE must be differentiated from high-intensity training, with the latter resulting in impaired cognitive performance (McMorris, 2016; Wang, Chu, Chu, Chan, & Chang, 2013). The main advantage of interval exercise (HIIE) is the abundant lactate production but limited catecholamine release and mental stress (Hashimoto et al., 2018). Interestingly, we have found an association between blood lactate concentrations and improvements in short-term visuospatial and long-term declarative memory. This observation has been recently brought to attention, revealing the critical role of lactate in cognitive enhancement and brain health after HIIE (Hashimoto et al., 2021). It has been previously demonstrated that lactate can cross the blood–brain barrier, and once attached to a specific receptor, it triggers multiple reactions in the brain (El Hayek et al., 2019; Proia, Di Liegro, Schiera, Fricano, & Di Liegro, 2016). Furthermore, Skriver et al. (2014) have found a correlation between systemic lactate release and the acquisition and retention of motor skills. Regarding its effects on metabolism, during HIIE, the brain becomes increasingly dependent on lactate supply (van Hall et al., 2009) in contrast to preferential glucose uptake in resting conditions. Cerebral lactate consumption rises once the blood lactate levels are above ≥2 mM (Rasmussen, Wyss, & Lundby, 2011), which the values far exceeded in our HIIE session but not in MIE. As we have highlighted above, one of the hypotheses of the cognitive improvement of HIIE versus MIE implies the mediator role of BDNF, which could be linked to increased lactate production during exercise. Along the same lines, El Hayek et al. (2019) have suggested that lactate released during exercise is transported to the brain, crossing the blood–brain barrier, where it induces BDNF expression. Curiously, this exercise-induced lactate shuttle to the brain has been shown to enhance visuospatial memory (El Hayek et al., 2019). Other effects of lactate on the central nervous system include the support of synaptic activity (Schurr, West, & Rigor, 1988), long-term potentiation and memory formation (Suzuki et al., 2011), and neuronal plasticity (Yang et al., 2014), all of which suggest that brain function, understood as cognitive performance, depends on the lactate metabolism in the brain. Taken together, these observations could be behind the associations we found between memory enhancement and higher lactate concentrations after the HIIE session.

When proposing the hypothesis that relates lactate and BDNF, it is worth considering the BDNF polymorphism. We have found a similar relative distribution between Val/Val and Met carriers (Val/Met or Met/Met) in our study to those previously reported (Hashimoto et al., 2008). Given that the presence of Val66Met could result in decreased levels of BDNF released in response to exercise (Nascimento et al., 2015), this SNP should be considered when analyzing the effects of exercise on cognition. In human subjects, some studies have reported an interplay between physical exercise and declarative memory influenced by the BDNF polymorphism, where a positive influence was only revealed in the Val/Val carriers (Canivet et al., 2015). However, divergent theories elucidating the effects of distinct SNPs on the exercise-cognition relationship exist. For instance, and in agreement with the findings above, the presence of valine in a gene sequence could predispose one to enhanced cognitive response following exercise, and this effect could be explained by the increased release of BDNF (Mang, Campbell, Ross, & Boyd, 2013). However, contrasting hypotheses favoring the opposite conclusion exist. More precisely, it has been suggested that Met carriers could experience exercise-induced cognitive gains to a larger extent, where exercise could make up for lower baseline levels of released BDNF (Moreau, Kirk, & Waldie, 2017). In our study, we could not find any association between the BDNF polymorphism with the cognitive response following exercise in young adults. Unfortunately, this observation does nothing but add up to the conflicting evidence on the role of BDNF polymorphism in the exercise–cognition relationship (de Las Heras et al., 2022). Along this line of thought, and in parallel with the findings by de Las Heras et al. (2022), this disparity in the reported results could indicate that, in fact, the cognitive gains associated with physical exercise are not dependent on the genetic profile, and all individuals could derive benefits from exercise on cognitive function.

Finally, we have attempted to determine if the differences in the cognitive response observed after HIIE and MIE depended on sex. In this regard, we have not found any discrepancies, and the trend of HIIE being the superior modality was true for both sexes. There are some indications that men release more BDNF both after acute exercise (Szuhany et al., 2015) and after a period of training (Szuhany et al., 2015), which could be translated into improved cognitive function. However, there is no agreement in the literature with regard to functional changes, with some studies observing a better cognitive response to aerobic exercise in women (Barha et al., 2017; Colcombe & Kramer, 2003), while others have found worse long-term outcomes in cognitive function after exercise programs in those studies with a higher percentage of female participants (Ludyga et al., 2020). This inconsistency could be explained by methodological differences between studies, including the preferential selection of older adults or major variations in the dose/intensity prescription of the chosen exercise type (Ludyga et al., 2020). Therefore, although we have not found any sex-dependent differences in our case, future research on exercise and cognition should contemplate equivalent samples of both sexes to understand the possible variations between them better.

This study has some limitations that must be considered when interpreting the results. First, we inferred the association between accelerated brain lactate metabolism and improved cognitive function from previous research (Tsukamoto et al., 2016). However, studies directly measuring brain lactate levels are required to test our hypothesis about the relationship between lactate concentrations and cognitive function. Second, given the large body of evidence on the effects of physical exercise on memory (Roig et al., 2013), our objective was to compare different intensities considering the role of possible moderators, such as lactate and BDNF polymorphism, in this relationship. However, just as in the study by Tsukamoto et al. (2016), we have not included a sedentary control condition; thus, we could not assess the ecological context where participation in physical exercise would have contrasted with a different condition. These alternative situations, in turn, could influence the cognitive response (Iuliano et al., 2015).

Moreover, the training load (a product of the intensity and duration of the exercise session) varies between experimental protocols, and we are aware that the magnitude of the training load will determine the physiological adaptations following an exercise bout. The reason for limiting both protocols to 20 min is founded in the previous research, where this timeframe has provided the most benefit for cognitive function (Chang et al., 2019; Chang et al., 2015; Oberste et al., 2019). Thus, once we have settled upon the optimal duration, we can only manipulate the exercise intensity, which would inevitably produce different loads and could be considered a limitation of the present study. However, the issue is the lack of previous evidence on the relationship between exercise load and cognitive function.

In future research, the focus should be placed on the examination of the dose–response relationship as it concerns the intensity-cognitive response link, but it is also fundamental to explore the remaining FITT (frequency, intensity, time, type) variables and the relationship between them (exercise load). Many questions still remain unanswered regarding the impact of the FITT dimensions, and, of course, we are still far from fully elucidating the implications of load in exercise-cognition research.

However, we also view our work as an important step towards increasing our comprehension of the exercise–cognition relationship in young adults. First, we have examined this relationship from a dose–response perspective, an aspect that has received less attention as a modifiable factor (Herold, Müller, et al., 2019). To augment our understanding of the possible mechanisms underlying the effects of exercise on cognition, we have also included the analysis of lactate and BDNF polymorphism. Lactate has been related to exercise intensity and BDNF polymorphism is a non-modifiable genetic condition; both were previously listed as possible modulators in the cognitive response to exercise, with, nonetheless, a lack of consideration in the relevant literature so far (Stillman et al., 2020). Finally, research to date has mostly failed to include all age groups. As such, children and older adults are preferentially selected as study populations. Meanwhile, adolescents and young adults have been the objective of far fewer studies (Stillman et al., 2020). Therefore, the inclusion of young people in our work contributes to the lacking evidence supporting the role of physical exercise in enhancing cognitive function in this age group and proposing the possible mechanisms underlying the exercise–cognition relationship (Stillman et al., 2020).

CONCLUSIONS

Our main findings suggest that HIIE is superior for enhancing memory compared to MIE. These positive effects, observed after HIIE but not after MIE, confer an important role to exercise intensity in magnifying cognitive response after acute physical exercise in young adults. Moreover, we have observed a positive association between blood lactate concentrations and memory improvements, suggesting that lactate released from the exercising muscle during HIIE may underlie the differences in cognitive function after two modalities. These observations apply to improvements in both short-term visuospatial memory, immediately after an exercise session, and long-term declarative memory. In the latter case, a session of HIIE during the memory consolidation phase resulted in enhanced formal memory retention and recall after 48 h. The number of recollected items after HIIE was far superior compared to MIE; furthermore, their total count correlated with the blood lactate concentrations after acute exercise. Finally, non-modifiable parameters such as biological sex and BDNF genetic polymorphism did not modulate the cognitive response to exercise.

AUTHOR CONTRIBUTIONS

Conceptualization, D.P. and E.C.; methodology, J.A.B.-F., A.R., and D.P.; software, J.A.B.-F. and A.R.; validation, J.A.B.-F. and A.R.; formal analysis, J.A.B.-F., A.R., and D.P.; investigation, J.A.B.-F.; resources, J.A.B.-F., A.R., and D.P.; data curation, J.A.B.-F. and D.P.; writing—original draft preparation, J.A.B.-F. and D.P.; writing—review and editing, A.R. and E.C.; visualization, D.P.; supervision, E.C.; project administration, D.P.; funding acquisition, E.C. All authors have read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Miguel Hernández University of Elche (protocol code UMH.CID.DPC.02.17 and approved on 12 October 2018).

INFORMED CONSENT STATEMENT

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

DATA AVAILABILITY STATEMENT

Not applicable.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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