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LONGITUDINAL STUDY OF THE NEUROPSYCHOLOGICAL CONSEQUENCES OF BINGE DRINKING IN UNIVERSITY STUDENTS: SIX-YEAR FOLLOW-UP

Carina Carbia Sinde

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EN NEUROCIENCIA Y PSICOLOGÍA, CIENCIAS DE LA SALUD

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(2) Contribución de Carina Carbia Sinde nos artigos en calidade de primeira autora; e

(3) Excelente calidade científica dos artigos publicados en revistas indexadas (Journal Citation Reports primeiro e segundo quartil).

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¿Recuerdas cuando soñábamos despiertos?

A congelar veranos enteros sin faltarnos a nosotros mismos.

A construir puntos cardinales y guardarnos los horizontes en los bolsillos.

A jugar a ser excesivos y arrancarnos los párpados,

ciegos de inmediatez.

A alimentar actos reflejos con puñados de hipérboles pasajeras.

Completamente desordenados por dentro.

Desorbitados.

Como cuerpos celestes que lo apostarían todo por tener trayectorias tangentes.

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Oliver Sacks, entre otras cosas, era un apasionado coleccionista de historias. De retratos. De esos que dejan huella. Y aunque suene muy a *cliché*, y detrás de mi curiosidad por la ciencia existan más razones, sus libros son una de ellas. Pero mucho más importante, es el hecho de que Oliver Sacks me ha permitido sentirme más cómoda con mi afición por capturar historias en lo cotidiano e ir regalando narrativas a las personas con las que me voy cruzando. Así, alegremente y sin que nadie me lo pida. Sólo para entretenimiento propio y coherencia interna.

Estos últimos años me han ofrecido algunos de los mejores retratos y las historias más irrepetibles de mi vida. A algunas ha costado verles el sentido, abstractas y obtusas. Pero seguían manteniendo su argumento y eso las hace respetables. Otras me han atrapado por completo. Como un único camino sin retorno, que una vez andado es imposible deshacer.

Mis directores de tesis tienen un papel importante en parte de estas historias. Fernando ha sido capaz de demostrarme que el entusiasmo puede incluso crecer con los años y que el humor es más fuerte que la burocracia. Dos cosas que siempre voy a admirar. Montse ha sido para mí un ejemplo de rigurosidad científica. Además, tiene el don de tener la palabra más amable disponible, para ti, incluso antes de que la necesites. Gracias a ambos por enseñarme más de lo que pueda caber en esta tesis.

La cercanía, la disponibilidad para ayudar y la inagotable energía son cosas que hacen de Paco alguien simplemente *awesome*. Disfrutar trabajando con Dudi, es decir una obviedad. Debo confesarle que es una de esas personas de las que siempre deseo que se me contagien muchas cosas. A todos los niveles. Gracias por mostrarme cómo hacer equilibrillos sobre peonzas de colores.

Salvatore y Elisa me demostraron que, aparte de la lluvia, belgas y gallegos (incluso italianos) tienen mucho en común. Me ofrecisteis una mezcla perfecta de

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El Comando ha sido terapéutico: los cafés, los amigos invisibles, la adolescencia alargada y la bendita procastinación. Hasta la paella. Todos me han sumado: Diego, Fran, Cris, Zeltia, Dudi, Marta, Pérez, Rocío, Úrsula, Carme, Alberto, Rubén, Carmela, Javi, Laura, Marcos, Sabela, Marina, Ángela y los *nuevos.* Por supuesto Samuel, por todas las (muchas) horas compartidas y por poder amenizarlas discutiendo sobre el particular juego de tronos del microbioma humano y otras incógnitas de la vida. Mis amigas, las de siempre: Olalla, Jessica y Tania. Olalla es uno de esos pilares que nunca fallan y eso ocurre en contadas ocasiones. Jessica, tú sabes tanto como yo de grises y de eternos retornos y no me imagino nada que pueda unir más. Tania es capaz de hacerte sentir que el tiempo no pasa y que la positividad está ahí, en la próxima esquina, esperando a que se fijen en ella. Y como esto no sigue un orden de ningún tipo, a mi perro Rocky le debo un "gracias" infinito. Por tener esa cualidad tan poco perruna, pero a la vez tan poco humana, de hacer que se te olvide el mundo cuando te mira.

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Esa, y mis rasgos obsesivos.

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RESUMEN

El *binge drinking* (BD) es un patrón caracterizado por la ingesta de grandes cantidades de alcohol concentradas en un breve período de tiempo y que por tanto, eleva la concentración de alcohol en sangre a 0,08 g/dl. Presenta su pico de prevalencia durante los primeros años de la veintena para decaer posteriormente. La evidencia científica ha puesto de manifiesto las consecuencias neurocognitivas que este tipo de consumo tiene en un cerebro todavía en desarrollo y, por tanto, más vulnerable a los efectos del alcohol. A pesar del creciente número de estudios, la gran mayoría de ellos son de carácter transversal, por lo que no es posible contrastar la relación de causalidad, ni determinar la evolución de las alteraciones detectadas. Es crucial, por tanto, llevar a cabo estudios longitudinales que permitan dilucidar los posibles efectos acumulativos de una trayectoria BD a lo largo de los años donde su prevalencia es máxima. Un segundo aspecto vinculado al seguimiento de las trayectorias es explorar la capacidad de recuperación del cerebro joven tras el abandono del BD. En el alcoholismo crónico existe amplia evidencia acerca de la recuperación de los déficits neurocognitivos, especialmente en relación a déficits de memoria episódica y de algunos déficits ejecutivos. Sin embargo, poco se conoce sobre la capacidad de mejoría de dichas alteraciones en jóvenes ex -BDs. Estos dos aspectos constituyen los objetivos principales de esta tesis doctoral, cuya muestra está constituida por estudiantes universitarios seguidos durante un período de seis años.

En primer lugar, se presenta en esta tesis una revisión sistemática de estudios neuropsicológicos (durante el período 2000-2016) cuyo objetivo es identificar los déficits cognitivos asociados al BD durante la adolescencia y la adultez temprana (**Artículo 1:** ***A systematic review of neuropsychological studies in young binge drinkers***). Pese al paulatino aumento de investigaciones científicas en torno al consumo intensivo de alcohol, ningún trabajo hasta el momento ha sintetizado de

forma sistemática los estudios neuropsicológicos con jóvenes BD. El objetivo principal de esta revisión sistemática fue, por tanto, cubrir ese vacío de conocimiento recopilando la evidencia existente acerca de las funciones afectadas y preservadas en esta población. Secundariamente, se analizaron las siguientes cuestiones: (I) qué variables del patrón de consumo se asocian consistentemente con los déficits neuropsicológicos; (II) cómo evoluciona el rendimiento cuando se mantiene el patrón; (II) si se aprecia reversibilidad de las alteraciones tras su abandono; y (IV) si existen diferencias de sexo en los efectos neurotóxicos del alcohol. La búsqueda bibliográfica se ha realizado en tres bases de datos (PsycINFO, Web of Science, and PubMed). Con base en una serie de criterios de inclusión previamente definidos, dos autores de forma independiente seleccionaron los artículos en cada una de las fases de este cribado, analizaron su calidad metodológica y han extraído los datos más relevantes. Un total de 27 artículos constituyeron la muestra final, los cuáles, en su mayoría, presentaron una calidad intermedia. Sólo cuatro incluyeron medidas repetidas de las variables neuropsicológicas. La revisión mostró que existe considerable evidencia para afirmar que el BD durante la adolescencia y adultez temprana se asocia con déficits de tipo ejecutivo, principalmente déficits inhibitorios. Los BDs podrían tener dificultades de flexibilidad cognitiva y en la auto-monitorización de la información en tareas de memoria de trabajo altamente demandantes. Sin embargo, un amplio número de estudios demostraron que los BDs no parecen presentar déficits en la capacidad para mantener o manipular información en tareas de span simple en memoria de trabajo. El BD en jóvenes se asocia con dificultades en la memoria episódica y posibles dificultades en memoria prospectiva. La evidencia en relación a la toma de decisiones es inconsistente y merece mayor atención futura. La atención, la velocidad de procesamiento y las habilidades de construcción visuoespacial parecen estar preservadas. En relación a las diferencias de sexo, tanto hombres como mujeres parecen presentar un perfil de alteraciones neuropsicológicas similares. Finalmente, la falta de estudios longitudinales no permite determinar hasta qué punto el mantenimiento de este

patrón prejudicial implica daños acumulativos, ni tampoco, el grado en que dichos déficits podrían ser recuperables con su abandono.

En segundo lugar, se presenta la parte empírica de esta tesis, constituida por tres trabajos que recogen los resultados del estudio longitudinal dirigido a determinar las consecuencias neuropsicológicas del mantenimiento del patrón de consumo intensivo de alcohol entre la adolescencia y la juventud temprana.

Como el objetivo era analizar las trayectorias de consumo, la muestra se clasificó en no-BD estables (aquellos que permanecían como tales durante todo el seguimiento); BD estables (aquellos que mantenían un patrón BD a lo largo de todo el seguimiento); y ex-BDs (aquellos que abandonaban el patrón BD en el primer o segundo seguimiento y permanecían con un consumo no-BD en los seguimientos posteriores). Además, para examinar los posibles cambios en el rendimiento neuropsicológico asociados al abandono del patrón y la duración del mismo, los ex-BDs se dividieron a su vez en dos trayectorias: ex-BDs a corto plazo (primer seguimiento con este estatus) y ex-BDs a largo plazo (más de un seguimiento con este estatus). Los participantes fueron seguidos durante un período de seis años (de los 18/19 a los 24/25 años), y se realizaron cuatro evaluaciones (una evaluación cada 22 meses de media). El número de participantes disminuyó a lo largo del seguimiento: 155 (76 no-BDs/ 79 BDs) en la primera evaluación; 93 (39 no-BDs estables/ 33 BDs estables/ 21 ex-BDs) en la segunda; 74 (33 no-BDs estables / 17 BDs estables / 24 ex-BDs) en la tercera; y 40 (16 no-BDs estables / 4 BDs estables / 20 ex-BDs) en la última evaluación.

El objetivo general del presente estudio es ahondar en la relación entre el patrón BD y el funcionamiento neuropsicológico en jóvenes universitarios seguidos durante un período de seis años. Así, se pretende describir el perfil neuropsicológico asociado a la persistencia o abandono del patrón BD, es decir, el agravamiento, mantenimiento o reversión/cese de los déficits. En concreto, se pretende analizar (I) la memoria de trabajo, dependiente de la red funcional frontoparietal y, más en concreto, del funcionamiento del córtex prefrontal dorsolateral (*Dorsolateral Prefrontal Cortex [DLPFC]*); (II) la memoria

episódica, dependiente del circuito prefrontal-hipocampal y (II) la toma de decisiones bajo condiciones de incertidumbre, dependiente del córtex prefrontal ventromedial y el orbitofrontal, que a su vez, están estrechamente conectados con el sistema límbico. En definitiva, todos ellos son aspectos del funcionamiento cognitivo que han mostrado ser especialmente vulnerables a los efectos neurotóxicos del alcohol. Para ello, se han propuesto una serie de objetivos específicos que se desglosan a continuación:

1. Determinar el patrón de evolución de las dificultades en relación con el mantenimiento de la trayectoria BD desde la adolescencia a la juventud temprana.

2. Determinar la reversibilidad de las dificultades neurocognitivas asociadas al abandono del BD a lo largo del tiempo.

3. Comprobar si existen diferencias sexuales en los efectos del patrón BD.

4. Valorar el posible efecto modulador de la edad de inicio de consumo de alcohol sobre el funcionamiento neurocognitivo.

Teniendo presentes estos objetivos se formularon dos hipótesis generales (comunes a los tres estudios) y varias hipótesis específicas (en relación a cada función cognitiva) con base en los resultados previos obtenidos en el marco de este proyecto y la evidencia científica.

1. Los participantes con una trayectoria estable de BD presentarán peor rendimiento neurocognitivo en memoria de trabajo, memoria episódica y toma de decisiones que aquellos participantes con una trayectoria estable no-BD.

2. El abandono del patrón BD conducirá a una mejora en el rendimiento cognitivo en memoria de trabajo, memoria episódica y toma de decisiones. Un mantenimiento prolongado de este abandono supondrá una progresiva mejoría cognitiva.

Hipótesis específicas:

Memoria de trabajo (*artículo 2*)

1.1. Los jóvenes con una trayectoria estable de BD presentarán menor rendimiento en la tarea de memoria de trabajo en comparación con los participantes estables no-BDs, especialmente en la parte más demandante de la tarea, en línea con la hipótesis compensatoria.

1.2. A pesar de mantener el patrón de consumo, los participantes BD estables mostrarán una mejora en la memoria de trabajo a lo largo del tiempo, compatible con la hipótesis del retraso neuromadurativo.

Memoria episódica *(artículo 3)*

2.1 En el paradigma de aprendizaje de una lista de palabras no relacionadas, los BD con trayectoria estable mostrarán dificultades relacionadas con disfunción prefrontal, mientras que en el paradigma de aprendizaje de historias los BDs estables mostraran dificultades en memoria episódica verbal compatibles con disfunción hipocapampal.

2.2. La progresión de las dificultades relacionadas con la actividad prefrontal mostrará una mejora a lo largo del tiempo, mientras que las dificultades relacionadas con el lóbulo temporal medial permanecerán estables o empeorarán, sugiriendo diferentes mecanismos explicativos (retraso neuromadurativo en dificultades prefrontales versus susceptibilidad hipocampal en déficits de consolidación de memoria episódica).

Toma de Decisiones *(artículo 4)*

3.1. Tanto hombres como mujeres mostrarán mejoras en el rendimiento en la tarea de toma de decisiones (Iowa Gambling Task [IGT]) durante

la adolescencia y la adultez temprana, asociado a una mayor eficiencia neuromadurativa.

3.2. Los hombres y las mujeres tendrán un rendimiento similar en el IGT en la dimensión de ganancias y las mujeres presentarán una mayor sensibilidad a la frecuencia de pérdida.

El primero de estos tres trabajos se centra en el rendimiento neuropsicológico en memoria de trabajo (**Artículo 2: *Working memory over a six-year period in young binge drinkers***). Este trabajo supone una continuación del realizado en nuestro grupo de investigación por Mota et al. (2013), quienes observaron que los jóvenes BDs, tras dos años manteniendo este patrón de consumo, presentaban un mayor número de errores perseverativos en una tarea de memoria de trabajo en comparación con los jóvenes no-BDs. Debido a la escasez de estudios longitudinales en adolescentes BDs, se desconoce cuál es la progresión a largo plazo de estos déficits tras el mantenimiento o el abandono del consumo. El objetivo de este estudio era examinar el rendimiento en memoria de trabajo asociado a la trayectoria BD durante la adolescencia y la adultez temprana tras seis años de seguimiento. Además, se analizaron las posibles dificultades en procesos específicos asociados a la memoria de trabajo y las posibles variaciones en tales déficits en función del grado de dificultad de la tarea. Se empleó una muestra inicial compuesta por 155 estudiantes universitarios de primer año. Los participantes se clasificaron según su trayectoria de consumo en estables no-BDs, estables-BDs y ex - BDs. La evaluación de la memoria de trabajo se hizo por medio de la tarea Self-Ordered Pointing Task (SOPT), con un total de cuatro evaluaciones. Los análisis estadísticos se llevaron a cabo mediante el software estadístico R. Se emplearon modelos lineales generalizados mixtos con el paquete lme4 Estos modelos realizan una estimación de máxima verosimilitud con una aproximación de cuadratura adaptativa Gauss-Hermitiana. Los GLMMs permiten el análisis de medidas repetidas lidiando con la correlación de la medida y la heterogeneidad intra-individual, lo cual proporciona un mayor poder estadístico en comparación con los modelos clásicos de regresión.

Los resultados mostraron que los participantes estables-BDs cometían más errores perseverativos y presentaban un menor span (en los bloques difíciles) en memoria de trabajo en comparación con los estables no-BDs. No se observaron diferencias en función del sexo. La edad de inicio de consumo de alcohol no mostró una asociación significativa con el rendimiento cognitivo. Mientras que las dificultades relacionadas con el span en memoria de trabajo mostraron cierta mejoría en el tiempo, los déficits perseverativos se mantuvieron constantes (sin cambios significativos) a lo largo de todo el seguimiento. Los participantes ex–BDs presentaron un rendimiento similar a los no-BDs. En resumen, estos resultados parecen indicar que un consumo BD prolongado se asocia a déficits en memoria de trabajo, que tras el abandono del patrón parecen experimentar cierta mejoría. El menor span en los bloques de mayor dificultad podría estar relacionado con la puesta en marcha de mecanismos compensatorios que permitirían una ejecución exitosa en la tarea hasta alcanzar cierto límite a partir del cual las demandas cognitivas son excesivas, lo que se traduciría en un pobre rendimiento en la tarea. La mejoría parcial de estas dificultades podría ser consistente con la hipótesis del retraso neuromadurativo; mientras que la estabilidad en el tiempo de los déficits perseverativos podría atribuirse a los efectos neurotóxicos del alcohol o constituir un factor de vulnerabilidad pre-existente.

El segundo de estos trabajos empíricos analiza la memoria episódica (**Artículo 3: *Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory*)**. El objetivo de este estudio era examinar el rendimiento en memoria episódica asociado a la trayectoria BD durante la adolescencia y la adultez temprana, dando continuación al trabajo previo con parte de la presente muestra donde Mota et al. (2013) observaron que los jóvenes BDs presentaban déficits en memoria episódica en comparación con los jóvenes no-BDs tras dos años de consumo. Este trabajo pretende arrojar luz sobre la progresión a largo plazo de estos déficits episódicos en relación al mantenimiento o el abandono del patrón BD. Durante un período de seis años se siguió a una muestra inicial de 155 estudiantes universitarios sin otros factores de riesgo. Los

participantes se clasificaron en tres trayectorias de consumo: estables no-BDs, estables BDs y ex –BDs. La memoria episódica se evaluó en cuatro ocasiones por medio del subtest Textos (Logical Memory, WMS-III) y el Aprendizaje Auditivo-Verbal de Rey (Rey Auditory Verbal Learning Test, RAVLT). El análisis estadístico de las trayectorias se realizó mediante modelos lineales generalizados mixtos. Los resultados mostraron que, en comparación con los estables no-BDs, los participantes BDs tendían a cometer más errores de intrusión en el RAVLT y presentaban menor rendimiento en el recuerdo inmediato y demorado de historias. Estas dificultades en memoria episódica permanecieron estables a lo largo del tiempo. Los participantes que abandonaron el patrón de consumo recientemente (BDs a corto plazo) presentaban aún las mismas dificultades en memoria episódica. Sin embargo, los ex –BDs a largo plazo mostraron un rendimiento similar a los no-BDs. No hubo diferencias en función del sexo o la edad de inicio de consumo de alcohol. En conclusión, mantener un patrón BD durante la adolescencia se asocia con déficits en memoria episódica que parecen experimentar una recuperación parcial tras un largo tiempo como ex -BDs. Estos resultados son consistentes con la especial vulnerabilidad del hipocampo a los efectos neurotóxicos del alcohol durante la adolescencia.

El último trabajo empírico de esta tesis se centra en la toma de decisiones **(Artículo 4: *Binge Drinking Trajectory and Decision-Making during Late Adolescence: Gender and Developmental Differences*).** La toma de decisiones es un proceso complejo que parece seguir desarrollándose durante la adolescencia tardía, con ligeras diferencias en función del sexo. Aunque el alcoholismo crónico se ha asociado consistentemente con déficits en la toma de decisiones, no está claro si esto se podría extender a los jóvenes con un patrón BD. El principal objetivo de este estudio fue determinar la asociación entre la trayectoria de consumo y la toma de decisiones desde la adolescencia tardía a la adultez temprana. En segundo lugar, dada la escasa literatura sobre el tema, se examinaron los cambios relacionados con el neurodesarrollo de la toma de decisiones durante este período y se analizaron las diferencias de rendimiento

entre hombres y mujeres. Se ha partido de una muestra inicial de 76 no-BDs, (40 mujeres) y 79 BDs (39 mujeres) de primer curso universitario. Los participantes se han seguido durante un período de cuatro años durante el que se evaluó su rendimiento en toma de decisiones mediante el Iowa gambling task (IGT), con un total de tres evaluaciones. Hasta donde sabemos, este sería el primer estudio con jóvenes BDs de carácter longitudinal en el que se emplean varias medidas repetidas del rendimiento en toma de decisiones. Los estudiantes se clasificaron en función de su trayectoria de consumo en estables no-BDs, estables BDs y ex-BDs. Los datos se analizaron con modelos lineales generalizados mixtos. Los resultados mostraron que el patrón BD estable no se asoció al rendimiento en la toma de decisiones y este resultado no variaba en función del sexo. El rendimiento mejoró para hombres y mujeres a lo largo del seguimiento, principalmente en los últimos bloques de la tarea. Las mujeres mostraron mayor sensibilidad a la frecuencia de pérdida que los hombres. En síntesis, los resultados sugieren que la toma de decisiones sigue mejorando durante la adolescencia tardía en ambos sexos, probablemente debido a cambios neuromadurativos. Las mujeres son más sensibles a la frecuencia de pérdida que los hombres, aunque ambos sexos consiguen seleccionar las cartas más ventajosas a largo plazo. El BD no parece estar asociado a déficits en este proceso cognitivo en jóvenes universitarios sin otros factores de riesgo (p. ej., psicopatología, policonsumo), si bien es posible que ocurra dicha afectación en consumos crónicos.

En resumen, los resultados de esta tesis mostraron que una trayectoria BD estable se asoció a dificultades de memoria de trabajo (menor *span* y más errores perseverativos) y memoria episódica verbal (menor recuerdo inmediato y demorado), pero no de toma de decisiones. Ambos sexos mostraron un rendimiento similar. A excepción de las diferencias en el *span* en memoria de trabajo que parecen mostrar cierta mejoría, las dificultades cognitivas presentaron un curso estable entre los que mantuvieron el patrón BD. Su abandono se asoció a una mejora del funcionamiento cognitivo. A corto plazo, se apreció una disminución de las dificultades ejecutivas, mientras que las

dificultades de la memoria episódica, especialmente los procesos de consolidación, parecen requerir mayor tiempo de abandono del patrón para mostrar mejoría. Los resultados son coherentes con la especial vulnerabilidad de las redes prefrontales y temporomediales a los efectos neurotóxicos del alcohol, durante este periodo de importantes cambios neuromadurativos.

Las conclusiones generales obtenidas del presente trabajo son las siguientes:

- Una trayectoria estable BD se asocia a dificultades en la memoria de trabajo (pobre *span* en los bloques más exigentes y errores perseverativos) y en la memoria episódica (pobre memoria inmediata y demorada), mientras que la toma de decisiones no parece verse afectada.
- A excepción del spam en memoria de trabajo (que parece mostrar una mejoría parcial), los déficits cognitivos presentan un curso estable.
- El abandono del patrón se asoció con una mejoría en los déficits cognitivos. Parece haber mejoras a corto plazo en los déficits ejecutivos, mientras que los déficits episódicos (especialmente en lo que respecta a los procesos de consolidación) parecen requerir un mayor tiempo sin consumo BD para experimentar mejoras visibles.
- Hombres y mujeres se comportaron de manera similar. Por lo tanto, los resultados no apoyan la hipótesis de la mayor vulnerabilidad de la mujer a los efectos del BD.
- La edad de inicio del consumo de alcohol no contribuyó a explicar el desempeño.

Palabras clave

Binge drinking, alcohol, neuropsicología, adolescencia, memoria

1

INTRODUCTION

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1. INTRODUCTION

The earliest evidence of alcohol consumption in human history dates back to the Neolithic period (McGovern et al., 2004) where the chemical residue of a fermented drink in a jar was found in a Chinese village, no less than 9,000 years ago. Throughout the centuries alcohol has continued to be ever present in our society and is now the most widely consumed psychoactive substance in the Western world (World Health Organization [WHO], 2014). Its use in excess is estimated to be responsible for 3.3 million deaths worldwide each year (WHO, 2017). Of particular concern is the excessive alcohol consumption among young people, which in turn, is linked to increased numbers of motor vehicle accidents, violence (especially domestic abuse), risky sexual behaviour and premature deaths (Marshall, 2014; WHO, 2017; Taylor et al., 2010). According to a recent report, 21% of students in Spain admit having had alcohol poisoning in the last 30 days, which is well above the European average (13%), on par with Austria and only lower than Denmark (32%) (Kraus et al., 2016).

The pattern of high-prevalence drinking among young people is known as binge drinking (BD) (Kuntsche, Kuntsche, Thrul and Gmel, 2017; Piano, Mazzuco, Kang, and Phillips, 2017). As its name suggests, it is the consumption of large amounts of alcohol in a short period of time, which usually leads to intoxication. It usually occurs on days close to the weekend and is intermittent, alternating between days of abusive use and days of minimal or no use (Parada et al., 2011b). BD is defined as the consumption that raises blood alcohol concentration levels to at least 0.08 g/dl (National Institute on Alcohol Abuse and Alcoholism [NIAAA],

2004); which in Spain would be equivalent to 6/5 (men/women) standard drinks.[1]

One in three young Europeans and Americans have ever followed this pattern (Kraus et al., 2016; Substance Abuse and Mental Health Services Administration [SAMHSA], 2017). According to the latest report of the Spanish Monitoring Centre for Drugs and Addiction, 32% of Spanish students between the ages of 14 and 18 acknowledged having partaken in BD (Survey on Drug Use in Secondary Education in Spain [ESTUDES], 2016). This high prevalence of BD has only decreased by 1% in the last twenty years (González-Alonso, 2015). Among young binge drinkers (BDs), there are some with even more extreme consumption. Although little data is available, it is estimated that 10% of young Americans consume more than 10 drinks per occasion and 5% consume more than 15 drinks on a single occasion (Patrick et al., 2013).

The onset of alcohol consumption occurs at an early age, with about 47% of European students reporting having consumed alcohol before the age of 13, which is similar to the Spanish average (i.e. 13.8 years-old) (ESTUDES, 2016; Kraus et al., 2016). Overall, European data indicates that the prevalence of BD among men and women is –in general- rather similar (Kraus et al., 2016), although the prevalence varies depending on age (ESTUDES, 2016). BD peaks during our early twenties, between the ages of 20 and 24 (Chen, Dufour, Yi, 2004; EDADES, 2015). As we approach adulthood, there is a decrease in the number of BD episodes (Figure 1). However, the percentage of young people who continue with

[1] In Spain, a standard drink is equivalent to 10 grams of alcohol, i.e., one fermented drink (e.g., one beer or one glass of wine). This value varies from country to country. Thus, while in USA and Portugal is equivalent to 14 grams of alcohol, in the UK it is equivalent to 8 grams and in Japan it corresponds to around 20 grams.

this pattern once they reach adulthood is notable (ESTUDES, 2016; Moure-Rodríguez et al., 2016), constituting a scarcely investigated high-risk group for whom interventions should be prioritized (Carbia, Corral, Doallo, Caamaño-Isorna, 2018).

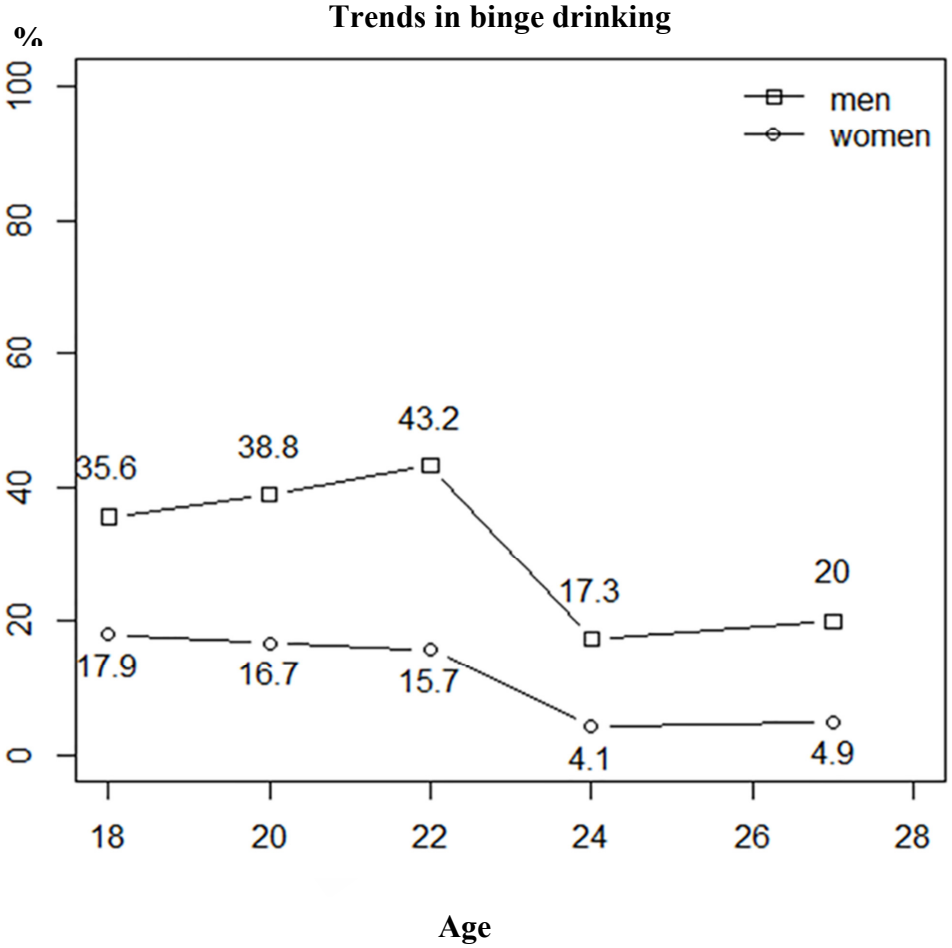

Figure 1. Prevalence of intensive alcohol consumption in Spanish university students from 18-19 years old to 27-28 years old (adapted from Moure-Rodríguez et al., 2016).

During adolescence and early youth, the brain is completing its maturation, and shows increased vulnerability to the neurotoxic effects of alcohol (Bava and Tapert, 2010). This, together with its high prevalence, makes BD a challenge to both society and to public health that has generated considerable scientific concern, especially within the last decade.

Adolescence is characterised by a period of marked changes at the psychosocial and developmental levels (Casey and Jones, 2010). Throughout this period, there are significant changes in the neurotransmission systems, mainly an increase in the density of the receptors of various neurotransmitters (e.g, GABA A receptors, NMDA receptors) and increased density of dopaminergic connections –a key neurotransmitter in the reward system (Volkow, Wang, Fowler, and Tomasi, 2012) - which will subsequently decline until it reaches normal adult values and stabilises (Crews, He, and Hodge, 2007; Guerri and Pascual, 2010). Although the overall size of the brain does not change during this stage, brain grey matter experiences a noticeable decrease mainly due to synaptic pruning processes of superfluous neural connections (Bava and Tapert, 2010). Conversely, white matter suffers a linear increase related to axonal mieleinization processes and an increase in the caliber of axons (Giedd, Keshavan, and Paus, 2008), particularly pronounced in frontoparietal areas (Bava and Tapert, 2010). Overall, the functional circuits of the brain experience remarkable development during adolescence, following a general principle of anatomical segregation and functional integration; that is, during childhood its organisation depends fundamentally on anatomical proximity, while the adult brain is characterised by functional networks with a widely distributed architecture (Fair et al., 2009; Vogel, Power, Petersen, and Schlaggar, 2010).

Such transformations have been associated with more efficient communication between brain regions and improved processing of the information needed to refine higher cognitive skills (Crone and Ridderinkhof, 2011). In this sense, the frontal, parietal and temporal cortical regions, together with other subcortical regions such as the striatum

or thalamus, are the last to complete their maturation while the sensory cortical areas are the first (Casey, Jones, Hare, 2008; Luna, Marek, Larsen, Tervo-Clemmens, Chahal, 2015). In this neuromaturational process there are differences associated with sex, suggesting that gonadal hormones have a key role in the different trajectories of cortical neurodevelopment and white matter (Blakemore Burnett, and Dahl, 2010). Men have a more pronounced increase/decrease in the white and grey matter (respectively) than women (Rubia, 2013). Women have earlier peaks of maturation in frontal, striatum, temporal and parietal areas (Gogtay and Thompson, 2010). Another widely demonstrated disparity is the greater size (faster growth) of the hippocampus in women and the amygdala in men during adolescence (Giedd, Raznahan, Mills, and Lenroot, 2012).

Due to the the dramatic anatomical and connectivity changes during adolescence, complex cognitive functions experience significant improvements. Performance in working memory tasks, inhibitory control, and cognitive flexibility continues to improve until early adulthood (Boelema et al., 2014; Diamond 2013; Taylor Barker, Heavey, and McHale, 2015). These functions are part of what are known as executive functions (see Diamond, 2013 for a review) and depend on the proper functioning of the prefrontal cortex (PFC) and frontostriatal circuits (Fuster, 2001). Decision-making improves linearly with age until reaching adult performance (Cassotti, Houdé, Moutier, 2011; Cauffman et al., 2010; Hooper, Luciana, Conklin, and Yarger, 2004). Episodic memory also continues to develop during late adolescence, a process that has been linked to the integration of the hypocampal-prefrontal circuit (Murty, Calabro, and Luna, 2016). Adolescence is simultaneously characterised by normative peaks in several features, such as reward-oriented behaviour, sensation-

seeking and risk-taking, which have been linked to experimentation with alcohol (Spear, 2000). These characteristics have been attributed to an imbalance between the early neurodevelopment of motivational systems and the late maturity of cognitive control (Geier, 2013).

As noted above, the relative immaturity of the adolescent brain makes it more vulnerable to the effects of heavy drinking. This has been pointed out in several studies with animal models in which it has been shown that adolescent rats with a BD consumption showed a greater structural and cognitive effect than adult rats (Crews, Mdzinarishvili, Kim, He and Nixon, 2006; Pascual, Blanco, Cauli, Miñarro and Guerri, 2007; White and Swartzwelder, 2005), especially in the prefrontal cortex (CPF) and hippocampus. In particular, animal model studies have shown that this pattern is associated with frontal cortical degeneration (Crews, Braun, Hoplight, Switzer and Knapp, 2000), neuroinflammation (Pascual, Pla, Miraño and Guerri, 2014) and myelin reductions in the prefrontal cortex (CPF) (Vargas, Bengston, Gilpin, Whitcomb, Richardson, 2014; Wolstenholme, Mahmood, Harris, Abbas, and Miles, 2017). In relation to the hippocampus, it has been observed that adolescent rats subjected to BD consumption show a considerable decrease in hypocampal neurogenesis (Broadwater, Liu, Crews, and Spear, 2014) and alteration of synaptic plasticity due to mitochondrial damage (Tapia-Rojas et al., 2017); accompanied by persistent memory deficits dependent on the hippocampus (Oliveira et al., 2015; Vetreno and Crews, 2015). In addition, these effects appear to persist in the long term (Coleman, He, Lee, Styner and Crews, 2011; Wolstenholme et al., 2017).

Most studies in humans with alcohol use disorder (AUD) have been focused on these two brain regions, namely the CPF and the hippocampus

(Silveri, Dager, Cohen-Gilbert and Sneider, 2016). Structural neuroimaging studies (Magnetic Resonance Imaging (MRI)) have consistently found a lower volume in the frontal lobe (Welch, Carson, and Lawrie, 2013), primarily in the prefrontal cortex in young AUDs with (De Bellis et al., 2005) or without psychiatric comorbidity (Medina et al., 2008). The evidence regarding the hyppocampus is less consistent. Lower hypocampal volume has been reported (De Bellis et al., 2000), especially in the left hemisphere (Nagel, Schweinsburg, Phan, and Tapert, 2005; Medina, Schweinsburg, Cohen-Zion, Nagel, and Tapert, 2007), in young AUDs with other comorbid disorders (e.g., outsourcing psychopathology). On the contrary, Fein et al. (2013), with a larger sample, found no hippocampal differences between AUD adolescents and controls. Studies that have investigated the effects of alcohol abuse or dependence on brain functioning using functional magnetic resonance imaging (fMRI) seem to indicate that young AUDs have alterations in the pattern of brain activity in regions involved in working memory processes (Caldwell et al., 2005; Park et al., 2011; Tapert et al., 2004), inhibitory control (Amlung, Sweet, Acker, Brown, and MacKillop, 2014) and episodic memory (Dager et al., 2013); as well as an overactivation to alcohol-related stimuli (Dager et al., 2014; Tapert et al., 2003).

Similarly, general population studies of young people with a BD pattern have described grey matter abnormalities both at the subcortical level (e.g., lower cerebellum volume, Lisdahl, Thayer, Squeglia, McQueeny, and Tapert, 2013) and at the cortical level (see Cservenka and Brumback, 2017 for a review). These alterations have been located mainly in the frontal lobe (Doallo et al., 2014; Heikkinen et al., 2017; Sousa, Sampaio, Marques, Gonçalves, and Crego, 2017), but also in the medial

temporal lobe (Kvamme et al., 2016; Squeglia et al., 2014; Wilson, Malone, Thomas, and Iacono, 2015) and parietal lobe (Pfefferbaum et al., 2016). Regarding white matter, there appear to be both macrostructural (Howell et al., 2013) and microstructural (Morris, Dowell, Cercignani, Harrison, and Voon, 2017) anomalies associated with BD. However, more studies are needed to clarify inconsistencies in structural outcomes both in relation to affected regions and the nature of the alteration (e.g., greater [Doallo et al., 2014] versus less [Heikkinen et al., 2017] volume in frontal regions). These alterations could be dose-dependent; in particular, it has been observed that the number of BD episodes negatively correlates to the thickness of the frontal and parietal cortex (Pfefferbaum et al., 2016) and brain volume (Lisdahl et al., 2013).

In recent years, a large number of functional neuroimaging studies have emerged exploring the effects of BD on brain activity patterns. These studies suggest that BD adolescents -although they do not show behavioural difficulties (with the exception of one study, Xiao et al., 2013)- they do present differences in brain activity (mainly greater activation in frontoparietal regions) in working memory tasks (Campanella et al., 2007), 2013; Squeglia et al., 2012), inhibitory control tasks (Campanella et al., 2016; Wetherill, Squeglia, Yang, and Tapert, 2013), and verbal learning tasks (Schweinsenburg, McQueeny, Nagel, Eyler, and Tapert, 2010; Schweinsburg, Schweinsburg, Nagel, Eyler, and Tapert, 2011). In turn, they seem to engage a greater number of brain regions that are considered to be irrelevant to the task. This abnormal pattern of activity has been interpreted in terms of functional compensation; that is, the involvement of normally inactive areas may be compensating for the compromised functioning of other regions, enabling a correct behavioral performance

(Cservenka and Brumback, 2017). BD has also been associated with alterations in the brain circuits linked to decision-making and reinforcement (e.g., reduced activation of the dorsal striatum [Jones, Cservenka, and Nagel, 2016], increased activation in the left amygdala and insula [Xiao et al, 2013], reduced activation in the left cerebellum [Cservenka, Jones, and Nagel, 2015]), as well as deficits in emotional processing (Maurage, Bestelmeyer, Rouger, Charest, and Belin, 2013). In addition, BDs show hyperactivity to alcohol-related stimuli, suggesting alterations in the mesolimbic and motivational circuits (Dager et al., 2014; Kreusch et al., 2015).

Electrophysiological studies using the Evoked Potentials (EPs) technique have shown that BD is associated with alterations in the brain electrical activity (mainly a greater amplitude) related to different cognitive functions: attention (N2/P3), working memory (P3), inhibitory control (P3-NoGo) and encoding processes in episodic memory (Crego et al.), 2009, 2010; Crego et al., 2012; Folgueira-Ares et al., 2017; López-Caneda et al., 2012; López-Caneda et al., 2013; Maurage, Mauro Pesenti, Philippot, Joassin, Campanella, 2009; Maurage et al., 2012; Petit et al., 2012; Petit, Kornreich, Verbanck, and Campanella, 2013). According to the results of our research group, these functional alterations seem to worsen with the maintenance of the pattern (López-Caneda et al., 2012; López-Caneda et al., 2013; López-Caneda et al., 2014). Recently, a study in which our research group has participated has found alterations in brain activity at rest (increased power in beta and theta oscillations) in the electroencephalogram (EEG) of the BDs, suggesting increased cortical excitability and possible difficulties in information processing (López-Caneda et al., 2017).

Despite the growing number of studies, the vast majority of them are of a cross-sectional nature, so it is not possible to determine causal inferences or examine the evolution of these alterations. It is in late adolescence that this pattern peaks - coinciding mainly with a person's university years- and it is not until early adulthood that it experiences a considerable decline, as demonstrated by epidemiological studies carried out by our research group (see Moure-Rodríguez et al., 2016). It is therefore crucial to carry out longitudinal studies to elucidate the possible cumulative effects of a DB trajectory over the years when its prevalence is at the highest level. A second aspect linked to the monitoring of trajectories is to explore the resilience of the young brain after the abandonment of the BD pattern. In chronic alcoholism there is ample evidence of recovery from neurocognitive deficits, especially in relation to episodic memory deficits and some executive deficits (Oscar-Berman et al., 2014). However, little is known about the recovery of these alterations in young ex-BDs. These two aspects constitute the main objectives of this doctoral thesis, a study of BD university students followed over a period of six years.

First, this thesis presents an in-depth systematic review of neuropsychological studies (during the period 2000-2016) aimed at identifying cognitive deficits associated with BD during adolescence and early adulthood (Article 1: *A systematic review of neuropsychological studies in young binge drinkers*). In addition, we analyze the evidence regarding other relevant drinking variables (e.g., age of onset); discuss potentials sexual differences regarding the effects of alcohol; and describe the reversibility of the neuropsychological difficulties after the abandonment of BD.

Secondly, the empirical part of this thesis is presented, consisting of three papers that discuss the results of a longitudinal study aimed at determining the neuropsychological consequences of maintaining the BD throughout late adolescence. The first of these three papers focuses on neuropsychological performance in working memory (Article 2: *Working memory over a six-year period in young binge drinkers*); the second on episodic memory (Article 3: *Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory*); and the last on decision-making (Article 4: *Binge drinking trajectory and decision-making during late adolescence: gender and developmental differences*).

The discussion integrates the results of the different studies conducted, comparing them to the findings of relevant literature to draw conclusions about the strength of the evidence. In addition, assumptions about the nature of deficits and the mechanisms underlying harmful alcohol consumption are further explored. Finally, a critical analysis is made identifying the limitations of the present thesis and some considerations are raised that may be of interest for future research.

1.2. ARTICLE 1

Carbia, C., López-Caneda, E., Corral, M., Cadaveira, F. (2018). A systematic review of neuropsychological studies involving young binge drinkers. *Neuroscience & Biobehavioral Reviews, 90,* 332-349.doi: 10.1016/j.neubiorev.2018.04.013 (IF=8.3; Q1)

https://www.sciencedirect.com/science/article/pii/S0149763417303846?via%3Dihub

2

RESEARCH APPROACH

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2. RESEARCH APPROACH

As previously stated, adolescence and early adulthood are periods of brain maturation characterised by a refinement of neuropsychological functions, such as working memory or decision-making (Diamond, 2013). These neuromaturational changes lead to a greater vulnerability to the neurotoxic effects of alcohol (Bava and Tapert, 2010). In the last decade, the number of studies published in this field has increased significantly, reflecting a growing concern about such a widespread -and even normalised- practice associated with neurocognitive difficulties, as described in the introduction.

Based on the need for prospective studies, this thesis is part of a longitudinal project on the neurocognitive consequences of heavy episodic drinking in university students. In addition to evaluating the neuropsychological performance, which is the objective of this thesis, the project also involves measuring the electrical activity of the brain (evoked potentials) associated with different cognitive functions and determining the neurostructural impact by means of magnetic resonance. The objectives and hypotheses have been formulated not only taking into account the previous literature on the subject, but also the previous data obtained in the successive evaluations of three cohorts of university students. The cross-sectional analysis of the baseline assessment with only the students of the first cohort is described in Parada et al. (2011a) (episodic memory) and Parada et al. (2012) (executive functions), and the first follow-up of this subset is described in Mota et al. (2013). In addition, data relating to decision-making (from the first to the third evaluation with all the cohorts),

which had not been explored in previous studies related to this project, is also analysed.

2.1. Objectives and hypothesis

The overall objective of this study is to explore the relationship between the BD pattern and neuropsychological functioning in young university students followed over a six-year period. Thus, it is intended to describe the neuropsychological profile associated with the persistence or abandonment of the BD pattern, i.e., the worsening, maintenance or recovery/ cessation of deficits. Specifically, it is intended to analyze (I) working memory, dependent on the frontoparietal functional network and, more specifically, the functioning of the dorsolateral prefrontal cortex (Dorsolateral Prefrontal Cortex [DLPFC]) (Diamond et al., 2013; Harding, Yücel, Harrison, Pantelis, and Breakspear, 2015); (II) episodic memory, dependent on the prefrontal-hipocampal circuit (Murty et al.., 2016) and (II) decision-making under conditions of uncertainty, dependent on the prefrontal ventromedial cortex and the orbitofrontal, which in turn, are closely connected to the limbic system (Brevers, Bechara, Cleeremans, Noël, 2013). In short, all of these are aspects of cognitive functioning that have been shown to be particularly vulnerable to the neurotoxic effects of alcohol. To this end, a number of specific objectives have been proposed, broken down as follows:

1. Determine the evolution of difficulties in relation to the maintenance of the BD trajectory from adolescence to early adulthood.

1.1. Verify whether the difficulties in working memory and episodic memory associated with BD in the first (Parada et al. 2012) and second

phase (Mota et al. 2013) of the study (subset of participants) are maintained, increased or reversed.

1.1.1. Determine the processes affected (e.g. monitoring, inhibition) and the role of task difficulty as a modulator in working memory performance.

1.1.2. Determine the profile of episodic memory impairment (e.g., dysexecutive vs. amnesic and affected processes [coding, consolidation, retrieval]).

1.2. Analyze the relationship between consumption trajectory and decision- making.

1.2.1. Examine possible developmental gender differences during adolescence and early adulthood in decision-making.

2. Determine the reversibility of neurocognitive difficulties associated with the abandonment of BD over time.

3. Examine sexual differences in the effects of the BD pattern.

4. Assess the possible modulatory effect of the age of onset of alcohol consumption on neurocognitive functioning.

With these objectives in mind, the following general (common to the three studies) and specific (in relation to each cognitive function) hypotheses were formulated based on the previous results obtained within the framework of this project and the scientific evidence within this topic.

General hypothesis:

1. Participants with a stable BD trajectory will have poorer neurocognitive performance in working memory, episodic memory and decision-making than those with a stable non-BD trajectory.

2. Abandonment of the BD pattern will lead to improved cognitive performance in working memory, episodic memory and decision-making. Prolonged maintenance of this abandonment will lead to progressive cognitive improvement.

Specific hypotheses:

Working memory (Article 2)

1.1. Young people with a stable BD trajectory will present poorer performance in a working memory task compared to stable non-BDs, especially in the more demanding part of the task, in line with the compensatory hypothesis.

This hypothesis is based on the following evidence: Despite the absence of behavioural differences, several studies have shown that BDs have increased brain activity in relation to non-BDs in working memory tasks -among others- (Campanella et al., 2013; Squeglia, Schweinsburg, Pulido, and Tapert, 2011; Squeglia, Pulido, et al., 2012), which has been interpreted in terms of increased cognitive effort and compensatory mechanisms needed to perform at the same level as non-BDs. Along the same lines, several electrophysiological studies seem to corroborate these results (Crego et al., 2012; López-Caneda et al., 2014). Therefore, if cognitive demands increase, stable BDs may not be able to compensate for their difficulties and manifest differences in performance.

1.2. Despite maintaining the consumption pattern, stable BD participants will show an improvement in working memory over time, compatible with the hypothesis of neuromaturational delay.

According to several structural studies, the BD pattern may be associated with a brain neuromaturational delay. According to these

studies, young BDs present a greater cortical thickness in left frontal regions (Sousa et al 2017; Squeglia, Sorg, et al., 2012), possibly indicating a reduced synaptic pruning and a lower degree of neurodevelopment. A study conducted with part of this sample (Doallo et al., 2014) showed that young BDs had a larger grey matter volume in the left dorsolateral prefrontal cortex (Brodmann areas 9 and 46), a region especially involved in working memory (its volume correlates positively to the number of errors in the SOPT). On the other hand, previous neuropsychological studies conducted by our research group showed a lower span on the BD group in the Digit Span test (WMS-III) (Parada et al., 2012). However, these differences disappeared after two years maintaining the BD pattern (Mota et al., 2013). This apparent improvement in working memory in BDs compared to same-age non-BDs, may be compatible with a neuromaturational lag, resulting in a delay in cognitive efficiency related to excessive alcohol consumption.

Episodic memory (Article 3)

2.1 In a list-learning paradigm of unrelated words, stable BDs will show difficulties related to prefrontal dysfunction, while in the story-learning paradigm stable BDs will show difficulties linked to episodic verbal memory, compatible with hypocapampal dysfunction.

The list-learning tasks and the story-learning tasks are two paradigms traditionally used to evaluate episodic memory. However, they are not entirely equal (Strauss, Sherman, Spreen, 2006). Efficient learning of unrelated stimuli requires the implementation of active coding strategies

(e.g., semantic organization or clustering), dependent on prefrontal-hyppocampal circuitry (Gershberg and Shimamura, 1995; Stuss et al., 1994). Thus, in patients with frontal dysfunction, a dysexecutive profile has been reported in list-learning tasks characterised by susceptibility to interference (Shimamura, Jurica, Mangels and Gershberg, 1995), intrusions (Lundervold, Halleland, Brevik, Haavik and Sørensen, 2015; Rouleau, Imbault, Laframboise and Bedard, 2001) and persistent errors (Alexander, Stuss and Fansabedian, 2003). The encoding and retrieval of contextualized material depends -to a greater extent- on the hyppocampal system (Frisk and Milner, 1990; Sawrie et al., 2001). Therefore, different alterations (hyppocampal or prefrontal) could give rise to different profiles in these two episodic memory tasks.

> *2.2. The progression of difficulties related to prefrontal activity will show an improvement over time, while difficulties related to the medial temporal lobe will remain stable or will show worsening, suggesting different explanatory mechanisms (neuromaturational delay linked to prefrontal difficulties versus hypocampal susceptibility linked to deficits in episodic memory consolidation).*

The approach of this hypothesis is based on the findings of a series of neurostructural studies (MRI) in young BDs (Doallo et al., 2014; Howell et al., 2013; Mashhoon et al., 2014; Squeglia, Sorg et al., 2012) suggesting that the neurotoxic effects of alcohol interfere with the expected developmental changes during early adolescence, causing a delay in brain neurodevelopment. Two previous neuropsychological studies with part of this sample (Parada et al., 2011a; Mota et al., 2013) showed that certain executive deficits (proactive interference) in list-learning tasks disappeared

after two years of maintaining the consumption pattern, which was interpreted in terms of an improvement or a delay in the expected cognitive efficiency in relation to same-age non-BDs. However, deficits in episodic memory in the story recall task remained stable, consistent with the special vulnerability of the hippocampus to the neurotoxicity of BD (Morris, Eaves, Smith and Nixon, 2010).

Decision-making (Article 4)

3.1. Both men and women will show improvements in performance on the Iowa Gambling Task (IGT) during adolescence and early adulthood, associated with increased neuromaturational efficiency.

Efficiency in decision-making continues to develop during adolescence (Cassotti et al., 2011; Hooper et al., 2004). Although only a few developmental studies have investigated performance during early adulthood, it appears that both men and women continue to experience refinement in decision-making at this stage of life (Cauffman et al., 2010).

3.2. Men and women will perform similarly in the gain dimension of the IGT and women will be more sensitive to loss frequency.

There is no general agreement on gender differences in decision-making. Some studies suggest that, in the particular case of the IGT, both sexes perform at the same level in terms of net gains (they are able to choose the most advantageous options in the IGT) although, women have a greater sensitivity to loss frequency, avoiding choosing cards with a high frequency of loss (Hooper et al., 2004; Van den Bos, Homberg, de Visser, 2013).

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3

METHODS

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3. METHODS

3.1. Participants

The sample was initially comprised of 155 healthy university students (76 men and 79 women) from various faculties of the Universidade de Santiago de Compostela (USC). Students were selected according to an anonymous questionnaire (administered in classrooms) that included the Alcohol Use Disorders Identification Test (AUDIT) (Babor, Higgins-Biddle, Saunders, and Monteiro, 2001) adapted to the Galician population (Varela, Braña, Real and Rial, 2005), together with items 10, 11 and 12 of the Alcohol Use Questionnaire (AUQ) (Mehrabian and Russell, 1978). Additionally, participants reported about drinking contexts, consequences and reasons for consumption, according to the questionnaire on alcohol consumption among young people in the Community of Madrid (Defensor del Menor de la Comunidad de Madrid, 2002). Importantly, there were several items about the use of other substances (cocaine, cannabis, tobacco etc.) and the frequency of consumption.

The classification of students according to their alcohol consumption was based on their response to the item number three of the AUDIT ("How often do you consume six or more drinks in a single occasion? Never/ Less than once a month/ At least once a month/ Weekly/ Daily") and a question related to the speed of consumption (number of drinks per hour). The BD pattern was defined as the consumption of at least six drinks on a single occasion (monthly or weekly) with a speed of three drinks or more per hour, which would lead to a blood alcohol concentration of 0.8 g/l or higher. Participants classified as ex-BDs were those who after abandoning

the BD pattern consumed up to six (or more) drinks per episode and less than once a month and/or consumed at a rate of two or fewer drinks per hour. The non-BD group was defined as never having consumed six drinks in a single occasion (or less than once a month) and having an alcohol intake rate of two drinks or less per hour. (Table 1)

Table 1. Patterns of alcohol consumption and definitions

Group	Drinks per occasion	Speed of consumption
BD	At least one per month	≥ 3 drinks/hour (BAC ≥ 0,8g/l)
Ex-BD	Never or less tan onces per month	≤ 2 drinks/hour (BAC ≥ 0,8g/l)
No-BD	Never or less tan onces per month	≤ 2 drinks/hour (BAC ≥ 0,8g/l)

As the objective was to analyze the drinking trajectories, the sample was classified into stable non-BDs (those that remained as non-BDs during the entire follow-up); stable BDs (those that maintained a BD pattern throughout the entire follow-up); and ex-BDs (those that abandoned the BD pattern at the first or second follow-up and remained with a non-BD consumption at the subsequent follow-up). In addition, to examine the possible changes in neuropsychological performance associated with the abandonment of the pattern and its duration, the ex-BDs were further divided into: short-term ex-BDs (first follow-up with this status) and long-term ex-BDs (more than one follow-up with this status). Participants were followed for a period of six years (18/19 to 24/25 years), and four evaluations were conducted (one evaluation every 22 months on average). The number of participants decreased throughout the follow-up: 155 (76 non-BDs/79 BDs) in the first evaluation; 93 (39 stable non-BDs stable/33 stable BDs /21 ex-BDs) in the second; 74 (33 stable non-BDs /17 stable

BDs /24 ex-BDs) in the third; and 40 (16 stable non-BDs /4 stable BDs /20 ex-BDs) in the last evaluation.

3.2. Procedure

Once classified according drinking patterns, participants were interviewed to obtain information about clinical and socio-demographic variables relevant to the study. In order to reduce possible confounding factors, the exclusion criteria described in Table 2 were applied. Participants were instructed not to use alcohol or other drugs for at least 12 hours prior to the neuropsychological evaluation and not to partake in BD episodes for at least 24 hours prior to the evaluation, to prevent possible effects of acute use and/or alcohol withdrawal. They were also instructed not to smoke or drink tea or coffee at least three hours before the experiment.

Table 2. Exclusion criteria.

- Alcohol abuse/dependence (DSM-IV-TR) or AUDIT ≥ 20
- Personal/family (1º and 2º degree) history of psychopathology or GSI > 90 percentile,SCL-90R
- Family history of alcoholism or substance abuse (1ºdegree relatives)
- Other drug use (except cannabis)
- Alcohol use the day of the evaluation
- Motor/sensory deficits
- Neurological disorders
- Unconciousness ≥ 20 minutes
- Medications that may interfere with cognition

In each of the four evaluations - all conducted at the Faculty of Psychology (USC) - the above-mentioned exclusion criteria were applied to select a sample of healthy university students without psychiatric comorbidity. For each new evaluation, only those participants who had underwent the previous evaluation were contacted, so that all participants included in the last evaluation had gone through the prior three evaluations. Participants gave their informed consent before collaborating in the study (for informed consent, see Annex I) and received financial compensation for their participation. The study has been approved by the USC Bioethics Committee (see Annex II), in accordance with the ethical principles of the Declaration of Helsinki.

3.3. Material

The instruments used to assess clinical history and neuropsychological performance are described below; for a detailed overview of the neuropsychological tests used in each of the four neuropsychological assessments, see Annex III. The tests and questionnaires were selected on the basis of their psychometric characteristics and their sensitivity to the detection of neuropsychological dysfunction, especially in a non-clinical population of university students.

3.3.1 Clinical History

Psychopathology

Details about personal or/and family history of alcohol use disorders and medical or psychopathological disorders were assessed with a translated version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), Individual Assessment Module (IAM) and Family History Assessment Module (FHAM), designed by the Collaborative Study

on the Genetics of Alcoholism (COGA) (Bucholz et al., 1994; Rice et al., 1995).

To detect psychopathological symptoms, the Symptom Checklist-90-R (SCL-90-R) questionnaire (Derogatis, 1983) was administered using the validated Spanish version (González, De las Cuevas, Rodríguez, and Rodríguez, 2002). In particular, participants were excluded when they had scores above the 90th percentile in the Global Severity Index (GSI) or in at least two symptomatic dimensions (e.g., anxiety and depression).

Alcohol Consumption

A score of 20 or higher in the AUDIT was adopted as the cut-off criterion to rule out possible alcohol abuse/dependence (Babor et al., 2001).

Impulsivity

During the interview, the Spanish version of the Barrat Impulsiveness Scale (BIS-11) (Patton, Stanford and Barrat, 1995; Oquendo et al., 2001) and the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ) (Zuckerman, Kuhlman, Joireman, Teta and Kraft, 1993; Gomà-i-Freixanet et al., 2004) were applied.

3.3.2 Neuropsychological assessment

Self-Ordered Pointing Test (SOPT), abstract design version (Petrides and Milner, 1982) (Article 2).

This test consists of a booklet of 108 sheets of abstract drawings. The test is divided into four blocks, each with a higher stimulus load (6, 8, 10, and 12 stimuli to monitor) and a total of three trials. The designs are repeated on each of the pages but with a different location. The participant

must select a different stimulus on each page, without repeating any of the previously mentioned stimuli. The following variables were recorded: total number of errors; perseverative errors (the same item as in the previous page); span (number of new elements reported before the first error); monitoring (total errors from the third page onwards in blocks three and four) and proactive interference ([(total errors in the third trial in blocks 3 and 4) - (total errors in the first trial in blocks 3 and 4)] / [(total errors in the third trial in blocks 3 and 4) + (total errors in the first trial in blocks 3 and 4))). The proactive interference score was categorized into four ranges from -1 to 1. The SOPT evaluates self-monitoring of information in working memory (Strauss et al, 2006). Performance in this task has been associated with the functioning of the dorsolateral prefrontal cortex (DLPFC) (Brodmann areas [BA] 46 and 9) (Petrides, 2000).

Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) *(Article 3).*

This task involves learning a list of 15 words that are not semantically related to each other (list A). Five consecutive rehearsals are carried out. In them, the experimenter reads the words aloud and asks the subject to say all the words he remembers after each rehearsal. A list of interference (list B) is then presented and recalled, followed by free recall of list A (Essay VI). After approximately 20 minutes, there is a free recall of list A. Finally, a recognition task is administered in which the subject must identify the words in list A from a total of 50 words (that include the words in list B, list A, and phonologically or semantically related words). The test assesses immediate and delayed recall, learning curve, recognition, and proactive and retroactive interference, and provides qualitative information on the type of errors (e.g., intrusions). The following variables were recorded: number of words in the first trial of list A (A I); total

number of words in the five trials of list A (total A); total number of words recalled of list B; number of words in immediate recall of list A (trial VI); number of words in delayed recalled trial (trial VII); intrusions (words that are not part of the list evaluated); proactive interference (the difference between the number of words remembered after the first presentation of list A and list B); retroactive interference (the difference between the number of words recalled in list A trial V vs. trial VI) and the number of words correctly recognized. Alternative versions of the task were used in the second and third follow-up. Performance in this task has been related to the prefrontal and temporomedial cortex (Mitrushina, Boone, Rozani and Delia, 2005).

Logical Memory subtest (Wechsler Memory Scale-III, WMS-III) (Wechsler, 1997). *(Article 3).*

In this task two short stories (A and B) are read to the participant, with a second presentation of the story B. After the oral presentation of each of them, the participant is asked to reproduce them as accurately as possible. After 30 minutes, there is a free recall trial (the stories are not read again to the participant). A recognition task is then administered with 15 questions (true or false) about each of the stories. The following variables were recorded: Logical Memory I or total immediate recall (the sum of the score of story A and the two presentations of story B, mainly reflecting encoding of verbal material); Logical Memory II or delayed recall (the sum of story A and B, mainly reflecting consolidation/recovery processes) and recognition (reflecting retrieval process rather than storage process, as opposed to free recall trials) (Strauss et al., 2006).

Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, Anderson, 1994) *(Artículo 4)*.

In this computerized task, participants must choose a card from four decks (A, B, C, and D) that differ in terms of gain and loss. The subject's goal is to make as much money as possible. The task consists of five blocks of 20 cards each. The participant does not know the characteristics of the cards (probability of gain or associated loss) and should therefore infer them gradually as the task progresses. When the participant selects a card, a message appears on the screen indicating the amount of money they have won and lost after that election. Cards C and D are considered advantageous because they involve long-term gains (low immediate gains but small long-term losses), while cards A and B are considered disadvantageous because they lead to long-term losses (high immediate gains but large long-term losses). Decks A and B are equivalent in terms of total losses, and C and D are equivalent in terms of total gains (see Table 3). The decks also differ in the frequency/magnitude of loss, cards A (disadvantageous) and C (advantageous) have a higher frequency of loss but these losses are small; however, cards B (disadvantageous) and D (advantageous) have a lower frequency of loss but these losses are large. Two dimensions were recorded: the gain dimension ([C+D]-[A+B]), which represents the preference of advantageous cards over disadvantageous; and the loss dimension ([B+D]-[A+C]), which represents the preference of cards with low loss frequency over cards with high loss frequency. The IGT evaluates affective decision-making under conditions of ambiguity or uncertainty where the probabilities of reinforcement or punishment are not known to the participant and has been mainly related to the functioning of

the ventromedial and orbitofrontal prefrontal cortex (Brevers et al., 2013; Clark, Cools and Robbins, 2004).

Table 3. Characteristics of the decks in the Iowa Gambling task

		A	B	C	D
Gain					
	Magnitude	+	+	-	-
	Frequency	+	+	+	+
Loss					
	Magnitude	-	+	-	+
	Frequency	+	-	+	-
Final outcome		-	-	+	+

3.3.3 Complementary tasks

Edinburgh Handedness Inventory (Oldfield, 1971): Test used to determine the manual dominance X. It consists of a number of questions in relation to the preference for one hand or another to perform certain tasks.

Vocabulary (WAIS-III; Wechsler, 1997): This test was used in the baseline assessment to estimate participants' intellectual level. The respondent should define 33 words presented in order of increasing difficulty. It has a high test-retest reliability (>90) (Strauss et al, 2006).

3.4. Statistical Analysis

Statistical analyses were carried out using statistical software R (R Core Team, 2015, version 3.1.1). Generalized linear mixed models (GLMMs) were performed with the lme4 package (Bates, Maechler, Bolker, and Walker, 2014), in which maximum log-likelihood was approximated by adaptive Gauss-Hermite quadrature (Brown and Prescott, 2014). GLMMs allow the analysis of repeated measurements by addressing measurement correlation and intra-individual heterogeneity ("random

effects", see Winter, 2013), which provides greater statistical power compared to classical regression models (Gibbons, Hedeker, and DuToit, 2010). Unlike other statistical analyses of repeated measurements, these models allow to use a different number of participants in each evaluation. The results are expressed in relative risks (RRs) together with a 95% confidence interval, which represents the range of values in which the outcome is observed at the population level. The RR is a coefficient that represents a ratio of averages of a given score (e.g., delayed recall score) in one group relative to another (stable BDs/non-BDs), and therefore requires a reference category (e.g., control group) to make comparisons. Values greater than one with significant intervals indicate the "presence" of a variable (more errors, more words remembered, etc.), while values below one reflect the "absence" of such a variable (lower span, fewer elements remembered, etc.). GLMMs can be applied to data with a non-normal distribution. Models adapted to a negative binomial distribution (function: glmer.nb) were used to obtain standard errors corrected for the overdispersion parameter, particularly regarding perseverative errors in the SOPT and perseverative errors and intrusions in the RAVLT. With the rest of the neuropsychological variables, models adapted to the Poisson distribution (function: glmer) were used. To allow statistical models to compute negative values, a constant value was added to those variables that included negative scores (e.g., gains and losses in the IGT and proactive interference in the SOPT).

The dependent variables were the scores of the neuropsychological tests, with the different individual observations in each follow-up as the first level and the students (all observations of each follow-up nested in each individual) as the second level. The independent variable was the

consumption trajectory. The models were adjusted for time and sex (and analysed separately by sex in Article 4). The effect of a number of variables was tested: frequency of cannabis use, frequency of tobacco use, age of onset and psychopathological symptomatology (SCL-90-R GSI score). First, a bivariate analysis was performed with each of the covariates. A multivariate analysis was then carried out in which all independent variables with significance greater than 0.2 were included. Non-significant covariates were removed from these maximum models as long as the coefficients of the independent variables did not vary by more than 10% and the value of the Bayesian information criterion decreased (Schwartz's Bayesian Information Criterion - criterion for model selection among a finite set of models -[BIC]).

In order to determine the progression of performance over time, separate models were used to compare baseline performance with the following assessments (and the different assessments between them). The performance of short-term ex-BDs versus long-term ex-BDs was also compared to analyse the effect of the duration of BD abandonment. In addition, and following a conservative approach, an adjustment was made for multiple comparisons (SidakSD) (see article 3) and the statistical software JASP (JASP Team, 2016) was used to carry out complementary Bayesian analyses (see article 4) to test the significance of the null hypothesis (Masson, 2011).

The classification of stable consumption trajectories is a strict classification that does not allow for transitions, for example, a non-BD participant in the first and second assessment who switched to BD consumption in the third assessment would be excluded from the analysis from that moment onwards, but it would remain for the previous time-

points. Therefore, although there were few cases with incompatible changes in consumption, this type of classification leads to a certain sample loss. Thus, to make sure that this fact did not influence the results in a relevant way, we carried out a statistical analysis with the same models that allowed transitions in the consumption trajectory, that is to say, it considered the subject in each temporal moment according to his consumption in that specific evaluation. The results obtained were similar, without significant changes. As a result, stable trajectories were used as it allows a better analysis of cumulative effects over time in a more intuitive manner.

4

EMPIRICAL STUDIES

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4. EMPRICAL STUDIES

4.1. ARTICLE 2

Carbia, C., Cadaveira, F., López-Caneda, E., Caamaño-Isorna, F., Holguín, S. R., Corral, M. (2017). Working memory over a six-year period in young binge drinkers. *Alcohol, 61,* 17-23. doi: 10.1016/j.alcohol.2017.01.013. (IF =2.78; Q2)

https://www.sciencedirect.com/science/article/pii/S0741832916301707?via%3Dihub

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4.2. ARTICLE 3

Carbia, C., Cadaveira, F., Caamaño-Isorna, F., Rodríguez-Holguín, S., Corral, M. (2017). Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory. *PloS one, 12*(2), e0171393. doi.org/10.1371/journal.pone.0171393 (IF= 2.81; Q1)

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0171393

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4.3. ARTICLE 4

Carbia, C., Cadaveira, F., Caamaño-Isorna, F., Holguín, S. R., Corral, M. (2017). Binge drinking trajectory and decision-making during late adolescence: gender and developmental differences. *Frontiers in psychology, 8,* 783. doi: 10.3389/fpsyg.2017.00783 (IF = 2.31; Q2)

https://www.frontiersin.org/articles/10.3389/fpsyg.2017.00783/full

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5

DISCUSION

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5. DISCUSION

This discussion is based on the four general objectives of the presented thesis that served as the cornerstone: (I) to determine the neurocognitive effects of BD maintenance and (II) alcohol withdrawal; (III) to analyze possible sexual differences; and finally, (IV) to examine the potential modulatory effect of the age of alcohol consumption onset. To this end, the results of the three empirical studies are integrated and analysed in relation to each one of the objectives and, within this scheme, each of the hypotheses proposed are discussed. The aim is to generate a comprehensive debate by placing the present results in the framework of the growing scientific literature. Finally, the possible mechanisms underlying alcohol-related neurocognitive deficits are described.

5.1. Anomalies in neuropsychological performance associated with the BD trajectory

The first objective of this thesis is to determine the neurocognitive consequences of maintaining the BD trajectory throughout adolescence and early adulthood. Overall, the results suggest that the maintenance of BD trajectory during this stage is associated with deficits in working memory and episodic memory, while decision-making does not appear to be affected. With the exception of difficulties in working memory span, cognitive deficits present a stable course over time. The results are consistent with the particular vulnerability of prefrontal and temporomedial

structures linked to the neurotoxic effects of alcohol during this period of significant neuromaturational changes.

Working Memory

Working memory involves maintaining and manipulating information online and is one of the latest cognitive processes in reaching adult efficiency. It depends, to a large extent, on a frontoparietal network in which the dorsolateral prefrontal cortex (DLPFC) is a fundamental node (Diamond, 2013; Harding et al., 2015). This cognitive function has been the most frequently studied (see article 1). Most neuropsychological studies that have investigated working memory have done so by means of span tasks (e.g., Direct and Inverse Digits [WAIS]). As the results of the systematic review included in this thesis show, the evidence supports that young BDs do not present deficits in their capacity to store, or even manipulate, the information in working memory in this type of simple span task. An example of this is the study by Boelema et al. (2015) where a large sample was followed for four years and it was found that, even after a prolonged BD maintenance, young BDs did not show increased difficulty with regards to the storage of information or short-term memory. Few studies have employed highly demanding work memory tasks in which the participant has to self-monitor (or self-order) a large number of items, in which he or she needs to resort to executive strategies that allow him or her to complement the limits of the working memory storage. Studies with self-ordered tasks, although there are few, seem to indicate that BD is linked to self-monitoring deficits in working memory (Scaife and Duka 2009; Townshend and Duka 2005).

Based on the above, we hypothesized that BDs would have difficulties in working memory in a self-ordered task (SOPT) and that they

would be especially noticeable in the most demanding part of the task (compensatory hypothesis). The results confirmed that a stable BD trajectory is related to deficits in working memory (study 2), which is consistent with previous literature. Specifically, BDs, compared to non-BDs, show a higher number of perseverative errors that could be related to a failure in the self-monitoring of information. In addition, the BD pattern is associated with lower span only on the most difficult blocks. BDs may be able to compensate for their difficulties only up to a certain extent (e.g., 8 items). From this point onwards the successful manipulation of information requires the use of active or more elaborate strategies.

This absence of difficulties, both in the less demanding part of the SOPT and in other less difficult working memory tasks (e.g., Digit Span (WMS-III) or N-back tasks) could be due to the existence of compensatory mechanisms that allow a correct performance in the task, as we hypothesized (Chanraud and Sullivan, 2014). A compensatory mechanism is a set of brain changes (e.g., hyperactivation of the regions involved in a task or recruitment of alternative neural systems) that allow or facilitate the execution of a task even though such neural systems are compromised (Chanraud and Sullivan, 2014). Compensatory mechanisms based on cognitive demands have been widely studied in aging (CRUNCH hypothesis, Reuter-Lorenz and Park, 2010) and, to a lesser extent, in chronic alcoholism (Chanraud, Pitel, Müller-Oehring, Pfefferbaum, and Sullivan, 2013). In both conditions there are a series of key factors such as educational level, cognitive reserve, or the difficulty of the task itself, which will influence the availability of an individual's brain resources (Chanraud and Sullivan, 2014).

Functional studies with BDs seem to support this neurocompensatory hypothesis. Thus, despite showing no difficulties in the task, the BDs present a greater activation of brain regions involved in the execution of the task or the recruitment of additional brain regions in cognitive functions such as working memory (Campanella et al., 2013; Schweinsburg, McQueeny, Nagel, Eyler and Tapert, 2010; Schweinsburg, Schweinsburg, Nagel, Eyler and Tapert 2011; Squeglia et al., 2011; Squeglia, Pulido et al., 2012) or inhibitory control (Wetherill et al., 2013). Electrophysiological studies also provide evidence along these lines, suggesting that greater amplitudes in some components of the evoked potentials associated with attention processes, working memory (P3b) and inhibitory control (P3-NoGo, P3-stop) observed in young BDs could respond to compensatory changes that, again, allow a behavioural execution at the level of non-BDs (Crego et al., 2012; López-Caneda et al., 2013; López-Caneda et al., 2014).

The longitudinal nature of our study provides valuable information on the progression of these deficits: perseverative errors showed a stable course throughout the follow-up, however, difficulties in span experienced some improvement; as hypothesized, BDs may present some neuromaturational delay. That is, despite maintaining a stable BD trajectory, participants seem to continue to gain efficiency in working memory at a later age than non-BDs who are the same age. The hypothesis of a neuromaturational lag has emerged from a series of structural studies (MRI) in young BDs (Doallo et al., 2014; Howell et al., 2013; Mashhoon 2014; Sousa et al., 2017; Squeglia, Sorg et al., 2012), which suggests the possibility that the neurotoxic effects of alcohol interfere with the expected brain developmental changes during early adolescence, causing a delay in such maturation. A structural MRI study with part of this sample found that

young BDs compared to non-BDs had a larger grey matter volume in the left dorsolateral prefrontal cortex (DLPFC). This structural anomaly, in turn, was associated with a higher number of errors in the SOPT task. That is to say, BD could disturb the synaptic pruning processes (i.e. increased cortical thickness, reduced neurodevelopment and, therefore, reduced neural efficiency). Synaptic pruning consists of a decrease in the total number of synapses which, as a result, translates into a lower brain volume and, together with the myelinization processes, is the basis for the adult refinement of the cortical networks and the corresponding cognitive processes (Spear, 2013). Possible neurodevelopmental delays may be more visible during adolescence than during early adulthood, where BDs may continue to gain cognitive efficiency despite the maintenance of BD.

However, not all studies point in this direction (e.g. Heikinen et al., 2017; Squeglia et al., 2014). The evidence provided by the structural studies is characterised by notable inconsistencies in the nature of the alterations. Numerous methodological factors may be involved in the apparent heterogeneity of the findings, including: small sample size, age differences between samples, lack of correction by multiple comparisons in statistical analyses, the definition of the BD pattern or psychopathological comorbidities (e.g., attention-deficit hyperactivity disorder is linked to reductions in frontal lobe cortical thickness (Shaw et al., 2006)) (Ewing, Sakhardande, Blakemore, 2014).

Apart from the studies of our research group, to date no other neuropsychological study of a longitudinal nature has been conducted that is focused on analysing the performance in working memory - which is understood as the ability to manipulate information online - with young BDs; therefore, it is not possible to compare the progression of the

difficulties with other studies. Further, it also cannot be ruled out that persistent errors may respond to deficits in the ability to inhibit task-related information (previous items), thus interfering with performance (Strauss et al., 2006).

Episodic Memory

Memory is the process by which we encode, store and consolidate information for later retrieval (Lezak, Howieson, Bigler, Tranel, 2012). Classically, memory is divided into short-term and long-term memory, which is then subdivided into implicit memory (priming and procedural memory) and explicit or declarative memory (episodic and semantic) (Strauss et al., 2006). Episodic memory refers to the recall of experiences or episodes along with their context (time and place) and depends on prefrontal-hyppocampal circuits (see, for example, Moscovitch, Cabeza, Winocur, Nadel, 2016 or Murty et al., 2016, for a review). Verbal episodic memory has traditionally been evaluated using two paradigms: word list-learning tasks and story recall, which involve slightly different cognitive processes. Learning unstructured word lists (e.g., RAVLT) requires the implementation of strategies (e.g., semantic organisation) to achieve adequate performance, which is primarily related to the proper functioning of the frontal lobe (Gersberg and Shimamura, 1995; Stuss et al., 1994). In this sense, patients with frontal injuries have demonstrated high susceptibility to interference (Shimamura et al., 1995) and perseverative errors (Alexander et al., 2003) and intrusions in word learning tasks (Lundervold et al., 2015; Rouleau et al., 2001); normally interpreted in terms of executive difficulties, in particular, problems in self-monitoring. Story learning (e.g., Logical Memory) requires memorising detailed information in a structured context and is more dependent on the

hyppocampus (Frisk and Milner 1990; Sawrie et al., 2001; Woodard, Goldstein, Roberts, McGuire, 1999). Therefore, the neurotoxic effects of alcohol in prefrontal or hyppocampal regions may give rise to different difficulties depending on the verbal memory tasks used.

The results of our study (study 3) confirmed the hypothesis that a stable BD trajectory is associated with deficits in episodic verbal memory. The BDs showed difficulties in immediate recall (encoding) and, especially in delayed recall (consolidation) in the story paradigm. In addition, BDs tend to have executive difficulties (intrusions) evidenced in a list-learning paradigm that, consequently, negatively impacts their performance in episodic memory. The deficits in episodic memory, as hypothesised, remain constant throughout the follow-up, without significant improvement or worsening. We cannot rule out the possibility that the absence of worsening difficulties, despite maintaining the BD pattern, is -in part- due to sample loss (which was considerable in the last follow-up) or even to other uncontrolled confounding variables such as the level of physical exercise (inducer of hyppocampal neurogenesis [Hueston, Cryan, and Nolan, 2017]) that could contribute to the decline or prevention of further cognitive impairment.

In summary, our results support those of previous neuropsychological studies. As observed in the systematic review (study 1), in list-learning paradigms, BDs present executive difficulties such as poor use of clustering strategies, (Winward, Hanson, Tapert, Brown, 2014) or perseverative errors (Sanhuenza et al., 2011). Studies of adolescents diagnosed with alcohol abuse/dependence indicate that this excessive alcohol use is associated with deficits in episodic memory and, particularly, in the delayed recall of information (Brown, Tapert, Granholm and Delis 2000; Brown and Tapert,

2004). In a ten-year longitudinal study, Hanson et al. (2011) followed adolescents with a history of alcohol and other drug abuse that varied in severity. The authors demonstrated that, specifically, it was young people with the longest history of alcohol consumption who had the worst performance in episodic verbal memory compared to other drinking/drug trajectories. Apart from our research group (Parada et al., 2011a; Mota et al., 2013), the only study to date that has employed a story learning task is that of Ferret, Carey, Thomas, Tapert, and Fein, (2013). These authors showed that alcohol dependence was associated with deficits in immediate and delayed recall of stories, which is consistent with our findings.

Episodic deficits may be associated with alcohol-induced neuroinflammatory processes mediated by the release of pro-inflammatory molecules (e.g., cytokines and chemokines) that appear to end up causing neural damage to the cerebral cortex and hyppocampus (Montesinos, Alfonso-Loeches, Guerri, 2016). During adolescence, there is a high rate of new neuron generation in the hyppocampus, much higher than during adulthood (Nixon and McClain, 2010; He and Crews, 2007). As a result, and as studies with animal models have shown (Broadwater et al., 2014; Crews et al., 2006; Taffe et al., 2010), intensive alcohol consumption appears to produce a massive loss of cells, which either could not be formed (inhibition of neurogenesis) or could not survive once formed (Morris et al., 2010; Nixon, Morris, Liput, and Kelso, 2010).

Moreover, these difficulties could be aggravated by the intensity of the BD pattern. In this vein, Nguyen-Louie et al. (2016) showed that those participants considered to be extreme BDs (more than 10 drinks in a single occasion) had the most pronounced episodic memory deficits, evidencing dose-dependent cognitive difficulties. However, it should be noted that in

this group, 23% of the participants had an alcohol use disorder in addition to regular cannabis use. Conversely, our results have not shown a significant dose-response effect, possibly due to the low variability of consumption within the BD group itself.

Decision-making

As detailed in the introduction, the neurodevelopment of the different cortical and subcortical regions typically undergoes differentiated maturational courses (Spear, 2013), which ultimately allow for the refinement of neuropsychological functions (Diamond, 2013; Geier and Luna, 2009; Luna, 2009; Luna, 2009). Thus, motivational systems show an early maturation compared to the relative immaturity of the brain systems in charge of cognitive control (Geier, 2013). This imbalance may explain some of the normative features of this stage of life such as greater sensitivity to reinforcement, a tendency to engage in risky behaviour or to make unthoughtful decisions (Crone, Duijvenvoorde, Peper, 2016; Geier, 2013; van Duijvenvoorde, Peters, Braams, Crone, 2016), such as unsafe sex or drug experimentation (Moure-Rodriguez et al., 2016).

Decision-making is a complex process that involves making a choice from a number of competing options, for which we usually assess the short and long-term consequences of each possible choice (Van den Bos et al., 2013). Decision-making is related to the activity of a network involving the ventromedial and obitofrontal prefrontal cortex, as well as other limbic system structures such as the amygdala (Brand, Labudda, and Markowitsch, 2006; Clark, Cools, Robbins, 2004). One of the most widely used neuropsychological tasks for evaluating decision-making is the IGT, which is considered a measure of affective decision-making or decision-making under conditions of uncertainty. That is, the participant must rely

on his or her own hunches or intuitions (implicit learning) to make a decision, in the case of this particular study, to choose the cards that provide the greatest long-term gains (Bechara et al., 1994).

According to our results, decision-making (evaluated with the IGT) seems to continue to develop during early adulthood in both sexes, coinciding with the results of Cauffman et al. (2010). This period has been less studied than adolescence or childhood itself, during which there has been continuous improvement in performance in the IGT (Cassotti et al., 2011; Cassotti, Aïte, Osmont, Houdé, Borst, 2014; Hooper et al., 2004; Huizenga, Crone, Jansen, 2007). As regards to the trajectory of alcohol, the results obtained contradict the hypothesis made. A stable BD trajectory is not associated with poorer decision-making performance (study 4). The evidence so far is certainly inconsistent (see study 1). In a similarly sampled study, Bø, Billieux, Landrø, (2016) reported that young BDs had no decision-making deficits, and were able to choose the most advantageous long-term cards at the IGT. However, three other studies reported different outcomes. According to Xiao et al. (2009), the BDs chose more disadvantageous cards overall. Yoo and Kim (2016) found this effect only in the last few blocks. Conversely, Johnson et al. (2008) reported similar performance in young BDs compared to non-BDs, as our results showed. These inconsistencies could be due to several factors. First, decision-making deficits may be linked to executive difficulties, especially in the latter part of the task (Kim, Johnson, Cilles and Gold, 2011; Noël, Bechara, Dan, Hanak, Verbanck, 2007). However, not all studies have controlled for an overall measure of executive performance (e.g., Yoo and Kim, 2016). Secondly, some studies did not establish inclusion criteria to ensure that participants did not have other psychiatric comorbidities related

to difficulties in this type of task, or even alcohol abuse or dependence (Goudriaan, Grekin, Sher, 2007; Johnson et al., 2008; Xiao et al., 2009). Finally, the operationalisation of task performance has varied across studies. Consequently, the relative weight of the gain and loss dimensions - for which there appears to be some neurofunctional differentiation (Levin et al., 2012) - , has not been the same in all cases.

In a somewhat different order, there are other types of neuropsychological tasks that, unlike the IGT, assess decision-making under risk conditions (e.g. Information Sampling Task (IST)). In these tasks the probabilities associated with the gains or losses ("risks") of the different options are known, therefore, it is not necessary for the participant to be guided by his intuitions to solve the task (Balogh, Mayes, Potenza, 2013). Under this paradigm, Bø, et al. (2017) showed that a greater tendency to make risky decisions (also referred to in the literature as reflection impulsivity [Balogh et al., 2013]) was associated with a greater severity of the BD pattern a year and a half later, while no association was found in relation to decision-making under conditions of uncertainty (IGT). A functional neuroimaging study showed that BDs had an altered response to reinforcement (i.e. reduction in brain activity in the dorsal striatum, in a risky decision-making task specifically associated with the degree of recent alcohol consumption. In addition, before starting the BD consumption, these same participants showed reduced frontoparietal activity when performing this task, suggesting not only post-consumption alterations, but also possible previous alterations that could constitute risk markers for future intensive consumption (Jones et al., 2016).

In general terms, and although the directionality of the relationship is not clear, the results seem to suggest that only young people with more

severe or chronic drinking trajectories have difficulties in decision-making tasks under conditions of uncertainty, such as chronic alcoholism (Brevers et al., 2014; Noël et al., 2007; Noël, Bechara, Brevers, Verbanck, Campanella, 2010). The paradigm of risky decision-making, although poorly explored, could provide a promising framework for BD consumption during a life stage characterised by numerous reckless decisions (Albert, Chein and Steinberg, 2013; Balogh et al., 2013).

Although the study of gender differences in decision-making is beyond the scope of this thesis, we were able to make several observations in regards to this intensely debated subject (van den Bos et al., 2013 for a review). In our study, both sexes were able to make advantageous choices and thus achieve a successful performance. However, as we hypothesised, women showed a greater bias towards the frequency of loss than men, i.e. they tended to choose fewer cards with a high frequency of loss, reinforcing the results found by Hooper et al. (2004) and van den Bos et al. (2013). According to these authors, the gender differences in performance in the IGT may be due to the fact that women seem to attend to various aspects of the task (long-term gain and frequency of loss); while men seem to focus only on the overall aspect of the task (long-term gain).

5.2. Neuropsychological consequences associated with the abandonment of the BD pattern.

The results of the empirical studies of this thesis show that the abandonment of the BD pattern appears to be associated with an improvement in cognitive deficits, supporting our initial hypothesis. This partial improvement already seems to be evident in the short term in relation to executive deficits (perseverative errors and poor span in working

memory and intrusions). In contrast, episodic memory deficits appear to require more time without excessive alcohol consumption before showing significant improvement. In particular, encoding (immediate recall) and consolidation (delayed recall) deficits continue to be present in participants who have only recently abandoned the BD pattern. It is only after a long time as ex-BDs that encoding and consolidation deficits seem to show partial improvement, although the latter (delayed recall) may be the most resistant to improvement. The consolidation of information in episodic memory depends fundamentally on the integrity of the temporomedial system (Woodard et al., 1999), reinforcing once again the idea of the special vulnerability of the adolescent hyppocampus (Nixon et al., 2010).

These results, as they relate to the abandonment of BD, are in line with other findings from our research group using part of this sample and analysing the neural functioning associated with inhibition (López-Caneda et al., 2014). In this electrophysiological study, the participants who abandoned the BD consumption showed an intermediate position between the control group and the BD group. In addition, Winward and collaborators conducted two neuropsychological studies following young BDs during a 1-month period of controlled abstinence. In the first of these two studies (Winward, Hanson, Bekman, Tapert, Brown, 2014), BD participants remained abstinent for four weeks and three neuropsychological assessments were performed (an initial one, one after two weeks and one at the end). These authors found that the ex-BDs showed improvements in performance in executive functions, verbal memory and visuospatial skills, although their performance was still poorer than that of the non-BDs. The only exception was performance in a visuospatial task (Cubes, WASI) where the ex-BDs performed at the level

of the non-BDs. In the second paper (Winward, Hanson, Tapert et al., 2014), a similar design was used but only one neuropsychological evaluation was performed at the end of the month of abstinence. The results showed that ex-BDs continued to have difficulties in flexibility and in the use of clustering strategies in verbal memory tasks. However, due to the lack of an initial evaluation before the period of abstinence, the absence of difficulties in the ex-BDs in other indices (verbal memory, working memory) are difficult to interpret. Generally, in chronic alcoholism, long-term abstinence leads to cognitive recovery accompanied by structural changes related to processes of brain reorganization and neural recovery or regeneration; however, some alterations, especially of executive-driven difficulties, tend to persist despite abstinence (Oscar-Berman et al., 2014).

In short, some improvement seems to occur after the abandonment of the BD pattern. More studies are needed to replicate the recovery of long-term deficits and to determine whether the abandonment of the consumption pattern could lead to a complete recovery (performance statistically equal to the non-BD group and different from that of the BD group) or to confirm whether some deficits are more easily recoverable than others (executive functions versus episodic memory), as suggested by the results of this thesis.

5.3. Sex-related differences regarding BD and neuropsychological difficulties.

A recurring question in scientific literature is whether there are sexual differences with regard to the neurotoxic effects of alcohol. Overall, the functional and structural studies related to chronic alcoholism indicate the existence of slight discrepancies in the pattern of alterations by sex,

possibly related to differences in compensatory mechanisms and/or vulnerability factors in men and women (Nixon, Prather, Lewis, 2014; Sawyer et al., 2017). On the other hand, neuropsychological studies seem to indicate that women with alcoholism have greater neuropsychological deficits than men (Nixon et al., 2014). Another factor that may contribute to the inconsistencies is the fact that there is still no agreement on basic assumptions about the pharmacokinetics of alcohol (e.g., if women achieve higher blood alcohol levels at equal ethanol doses than men or the effect of the menstrual cycle) (Nixon et al., 2014; Ruiz and Oscar Berman, 2013). Thus, the accumulated evidence is not sufficient to support the hypothesis of women's increased susceptibility to the prolonged effects of alcohol consumption (Nixon et al., 2014; Ruiz and Oscar Berman, 2013).

As for the BD pattern, the neurostructural evidence regarding sex differences is also inconsistent. Some studies have found sex-related abnormalities, specifically lower volumes in frontal, temporal, and subcortical regions in male BDs compared to controls, while female BDs have higher volumes in these regions (Kvamme et al., 2016; Squeglia, Sorg, et al., 2012). In contrast, other results reported similar structural alterations in both sexes (Mashhoon et al., 2014; Squeglia et al., 2014), even after maintaining a BD trajectory for 10 years (Heikkinen et al., 2016). Similarly, functional studies, both those using functional magnetic resonance imaging and those using electroencephalography, appear to yield a similar conclusion; although some have reported different patterns of brain activity in men and women (Petit et al., 2013; Squeglia et al., 2011; Watson, Sweeney, Louis, 2014), most agree that there appears to be no increased vulnerability to the BD pattern on the basis of sex.

The results of the empirical studies of this thesis show similar cognitive difficulties in both sexes. These results coincide with those provided by neuropsychological studies to date (see study 1), supporting the notion of a similar cognitive impairment profile in men and women. However, it is possible that both the cross-sectional nature and small sample size of most studies, in conjunction with the different neuromaturational trajectories in men and women, may contribute to camouflaging possible gender differences. In addition, few neuropsychological studies have proposed the role of sex as an objective of analysis per se; beyond its use as a covariate (see study 1).

5.4. Age of onset of alcohol use as a moderator variable.

The onset of alcohol consumption at an early age is an important risk factor for BD during adolescence (Liang and Chikritzhs, 2013; Moure-Rodríguez et al, 2016), as well as for developing alcohol abuse or dependence in adulthood (Dawson, Goldstein, Chou, Rouen, and Grant, 2008; DeWit, Adlaf, Offord, and Ogborne, 2000; Hingson, Heeren, and Winter, 2006), engaging in risky sexual behaviour, suffering accidents or manifesting psychopathological symptoms during late adolescence (Carbia, Corral, García-Moreno, Cadaveira, and Caamaño-Isorna, 2016; Hingson, Heeren, Jamanka, and Howland, 2000; Zernicke, Cantrell, Finn, and Lucas, 2010).

As for the relationship between the age of drinking onset and cognitive performance, none of the empirical studies presented in this thesis demonstrate any association. Simply the age of alcohol onset by itself is probably a relatively nonspecific variable compared to the age of regular drinking onset or the age of onset of BD. On the other hand, as is

usually the case with retrospective self-report variables, this variable is susceptible to being affected by the so-called "telescope effect", a bias that refers to the inaccuracy or lack of precision of people's estimates of past events (Janssen, Chessa, and Murre, 2006; Sartor et al., 2011). In this sense, previous neuropsychological studies that examined the effects associated with the early age of onset of the BD pattern have found that it was associated with worse performance in attention (Winward, Bekman, Hanson, Lejuez, Brown, 2014) and visuospatial memory (Goldstein, Dery, Pilgrim, Ioan, Becker, 2016). A longitudinal study showed that an early age of onset (age of onset of alcohol use and age of first binge drinking episode) was a predictor of increased numbers of blackouts over three years, controlled for the number of BD episodes (Marino, and Fromme, 2016). In short, these results seem to suggest that starting to drink alcohol heavily at an early age may have a detrimental effect on neurocognitive functioning (Article 1). In any case, more studies are needed to determine the effect of the age of onset of the BD pattern, both in terms of cumulative damage and the possible existence of critical periods of neuromaturational vulnerability during early adolescence (Spear et al., 2015).

5.5. Possible mechanisms associated to the neurocognitive impact of BD consumption.

Currently, the mechanisms by which alcohol causes damage to the adolescent brain are still not fully elucidated. One mechanism that has been shown to explain neurodegenerative damage in chronic alcoholics is glutamatergic excitotoxicity, meaning the pathological process by which a cell is damaged after being over-stimulated by excitatory neurotransmitters such as glutamate (Crews et al., 2015). Thus, chronic consumption of

ethanol appears to inhibit NMDA (N-methyl-D-aspartate) glutamatergic receptors, and after alcohol withdrawal, deregulation characterised by excessive excitability would occur (Crews and Nixon, 2009). However, this mechanism does not seem to explain the damage caused by BD consumption, where, presumably, the brain damage occurs during the intoxication itself and not during the withdrawal phase (Crews and Nixon, 2009). Alcohol is also capable of inhibiting cerebral neurogenesis during intoxication, contributing to neurodegeneration through the loss of new neurons that have not yet being formed (Nixon and McClain, 2010), this mechanism of neurogenesis regulation could be related to inflammatory processes (Nixon et al., 2010).

Neuroinflammation is the mechanism that has had considerably more research devoted to it within the last decade (Guerri and Pascual, 2010) and studies indicate that alcohol may exert its neurodegenerative effect through the neuroimmune system both through mechanisms of direct interaction with the brain and through peripheral inflammation (see Figure 2 for a schematic representation). First, alcohol generates intestinal inflammation through different pathways, mainly changes in the intestinal microbiota and intestinal hyperpermeability also known as "leaky gut" (Bishehsari et al., 2017). This increased intestinal permeability allows a number of bacteria to enter the bloodstream, triggering an inflammatory response and causing the release of pro-inflammatory cytokines[2] (Crews et al., 2015; de Timary, Stärkel, Delzenne, y Leclercq, 2017). Consequently, the inflammatory response ends up triggering a cascade of mechanisms that produce additional inflammation and damage to various organs, primarily the liver and brain (Bishhesari et al., 2017; Leclerq et al., 2012).

[2] Grupo de moléculas, producidas principalmente por las células inmunes, que regulan las reacciones inflamatorias (véase para una revisión, Crews et al., 2015).

Alcohol dependence appears to be associated with high intestinal permeability and alterations in the composition of the intestinal microbiota which, in turn, appear to be associated with increased levels of anxiety, depression and craving (Leclercq, De Saeger, Delzenne, de Timary, and Stärkel, 2014). Evidence suggests that even a single BD episode in adults can increase plasma cytokine levels, triggering peripheral neuroinflammation (Bala, Marcos, Gattu, Catalano and Szabo, 2014) that seems to end up affecting brain regions such as the prefrontal cortex and the hyppocampus (Ward, Lallemand and Witte, 2014), ultimately resulting in worse cognitive performance (Orío et al., 2017).

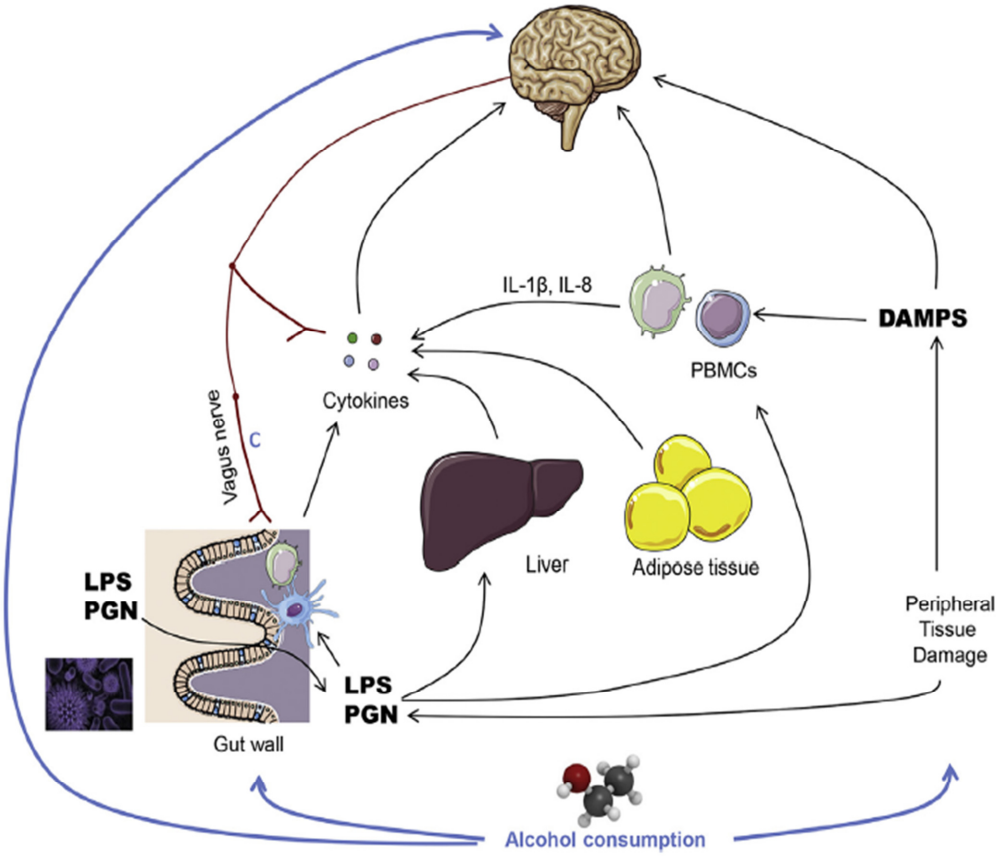

Figure 2. Schematic model of the intestine-brain interaction in relation to alcohol (from Timary et al., 2017, with permission from Elsevier, Neuropharmacology, Licence

426428281318934). Alcohol induces hyperpermeability in the intestinal epithelium ("leaky gut"). As a result, pathogens are released into the bloodstream, which via endotoxins (e.g. lipopolysaccharide (LPS)), trigger the activation of the immune system by releasing pro-inflammatory cytokines (e.g. tumor necrosis factor alpha [TNF-α], interleukin 8[IL-8]), which, in turn, trigger further inflammation in the liver and brain. Brain-intestine interactions may occur via two-way pathways, for example, through the vagus nerve.

The interaction between the intestine and the brain or, the “gut-brain axis”, (Cryan and O'mahony, 2011) is still an enigmatic topic that has fully captured the interest of the neuroscientific community in various fields, such as stress (Foster and Neufeld, 2013); psychopathology during adolescence (Borre et al., 2014) and, more recently, alcohol abuse (Leclerq et al., 2014). Intestinal dysbiosis may contribute to the symptomatology of alcohol addiction by interacting with the cerebral system's stress response, sleep phases, or even social skills (de Timary et al., 2017). It is possible that this brain-intestine axis hides some of the keys to a better understanding of the pathophysiological process behind the development of alcohol addiction (Crews et al., 2015).

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LIMITATIONS

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6. LIMITATIONS

Firstly, and with regard to the design of the study, the main limitation of this thesis is the lack of measurements prior to the onset of the BD, which prevents the establishment of causal relationships. Therefore, we cannot rule out that some of the difficulties observed, especially the executive ones, are not (at least to some extent) a premorbid characteristic. At a structural level, anomalies prior to alcohol consumption have been reported, specifically lower cortical volume in frontal regions in those adolescents who only years later began to drink intensively (Squeglia et al., 2014). Several functional studies suggest the existence of differences in brain activity in working memory (Squeglia, Pulido, et al., 2012) and cognitive inhibition (Norman et al., 2011; Wetherill et al., 2013) prior to a BD pattern. In particular, the results point to lower activity in frontoparietal regions prior to consumption, which could therefore be a risk factor. On the contrary, once the BD has started there appears to be higher activity in these regions as a result of the consumption itself (Cservenka and Brumback, 2017).

Three neuropsychological studies from Peteers' group and collaborators specifically address this issue. According to these authors, poorer working memory performance (SOPT) in adolescents who had not initiated drug use is an important predictor of both the onset of alcohol use and the BD pattern, which could lead to a vicious circle in which subsequent use would cause greater deficits, increasing the likelihood of developing alcohol abuse (Peeters, Vollebergh, Wiers, Field, 2014; Peeters et al., 2015). However, it should be noted that both studies were conducted using samples that included participants with externalising

psychopathological problems (e.g., attention deficit hyperactivity disorder). Recently, the same research group showed that poor self-control (measured by self-report) at age 11 was the best predictor of increased alcohol consumption four years later, especially among adolescents who were themselves hypersensitive to reward therefore presented poor decision-making performance (Bangor Gambling Task) (Peeters, Oldehinkel, and Vollebergh, 2017). It should be noted that, again, 66% of the participants in this study had psychopathological symptoms. Applying predictive algorithms (machine learning), Squeglia et al. (2017) showed that a combination of neurocognitive and neuroanatomical indices along with other characteristics (positive expectations regarding alcohol, externalised psychopathology, high socioeconomic status) were able to predict which of the 12 to 14-year-olds (who had not yet started to consume alcohol) would engage in heavy drinking at the age of 18. According to the authors, poor performance in executive functions and faster reaction times in sustained attention tasks (suggesting higher levels of impulsivity) were predictors of earlier alcohol onset. Lower cortical thickness and cortical hypo-activation in a working memory task during early adolescence were found to be important predictors of heavy alcohol use by the age of 18. Another study from the same group (Brumback et al., 2016) showed that reduced thickness of the dorsolateral prefrontal cortex and the frontal inferior cortex in early adolescence predicted both externalising psychopathology and future BD consumption. Overall, the results suggest the existence of cognitive abnormalities prior to BD that appear to act as vulnerability factors both in relation to initiation and escalation of alcohol consumption. In turn, BD would lead to increased neurocognitive involvement that could contribute to perpetuating this excessive use of alcohol. However, more replication studies, especially with adolescents without psychopathological

symptoms, are needed to confirm which specific neurocognitive characteristics contribute to the increased vulnerability of young people to this consumption pattern.

Secondly, another possible weakness of this study is the fact that the consumption trajectories were characterised according to the AUDIT, a questionnaire that evaluates alcohol consumption within the previous 12 months. Ideally, it would be useful to have at least one annual assessment (as our evaluations were every 22 months approximately), in order to have more accurate information and, in particular, to be able to track the consumption of those who had abandoned the BD pattern more closely. Even though there is an undocumented time period, we considered a participant's overall six-year consumption trajectory to be a sufficient measure to characterise the progression of problems associated with intensive consumption or cessation.

The third limitation of this study has to do with the representativeness of the population. The control of confounding variables such as cannabis use or psychopathology helps us to identify more clearly the neurocognitive deficits exclusively related to the BD pattern. However, it could also be an obstacle as it effectively circumscribes the target population to a subgroup: the group of young university students without other comorbidities; which is probably the subgroup with the least severe neurocognitive compromise and fewest associated complications.

Another relevant limitation is the loss of sample throughout the follow-up. This disadvantage, inherent in any longitudinal design, affects mainly the last evaluation (Article 2 and Article 3). To try to maximize the potential of the available data, we have chosen to apply GLMMs (R software) that, unlike classic repeated measurement analyses, are capable

of modeling trajectories with a different number of participants in each assessment (Gibbons et al., 2010). In addition to dealing with missing data, these models offer greater statistical power than traditional methods of analysis of variance, as they are able to compute the correlation of individual response and heterogeneity (random effects) in a study with numerous repeated measures (Winter, 2013). That is to say, the response of an individual is subject to variations that respond both to an average population trend and to individual differences. When a subject's response is repeatedly measured over time, this individual heterogeneity, along with possible measurement errors (response inter-dependence), results in important deviations in the average response pattern that only address characteristics of a subject and not of a population. Thus, by being able to adjust the deviation and interdependence of responses at an individual level, the models allow for a better statistical characterisation of the observed data. Despite the drawback of sample loss, we believe that our results are still a valuable contribution to the scientific literature, particularly in light of the lack of studies with consumption trajectories that evaluate both the maintenance and the abandonment of BD. However, we believe that the results need to be interpreted with caution and we hope that they will be replicated using larger samples.

An unavoidable consideration is the fact that in the absence of validated alternative versions of neuropsychological tests (with the exception of the RAVLT) the results may be affected to some extent by practice effects, which could have an impact on the progression of neuropsychological difficulties. For example, the absence of changes in the progression of episodic memory deficits in BDs over time may -to some extent- mask a cognitive decline. However, this would affect all groups

equally. In addition, we consider that as neuropsychological tests were administered approximately every two years, a sufficiently long period of time has elapsed to not imply a relevant practice effect, especially taking into account the difficulty of the tasks.

A limitation that directly affects the discussion of the results of this thesis, and the scientific literature in general, has to do with what is known as publication bias or the tendency to facilitate or favour the publication of significant results over non-significant ones (Ioannidis, Munafo, Fusar-Poli, Nosek, and David, 2014). Fortunately, more and more efforts are being made to correct the negative impact of this bias by creating journals or sections aimed solely at the publication of "negative" results or simply by raising awareness within the scientific community that science is built on transparency and replication.

Finally, as a reflection, it is necessary to be aware that this study, by using only neuropsychological tests, gives a limited vision of brain functioning. Future progress in the knowledge of the neurocognitive effects of BD must be not only quantitative, that is to say, replicating the existing results, but also qualitative, involving an interdisciplinary effort and bringing together results from different techniques and disciplines (neuropsychology, neuroendocrinology, etc.).

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FUTURE CONSIDERATIONS

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7. FUTURE CONSIDERATIONS

Future studies are expected to resolve the dilemma surrounding the causes and consequences of BD. In the immediate future, it is essential to consolidate and advance our understanding of the effects of heavy drinking, replicating existing results, elucidating the various controversies and delving deeper into the nature of the anomalies. Similarly, a future objective is to analyse the progression of deficits and especially the long-term recovery of deficits. At the same time, it would be useful to study the characteristics of young people who voluntarily give up this pattern of consumption during a period in which BD tends to peak. An additional objective of this longitudinal approach is to clarify the existence of possible windows of vulnerability where the effects of BD may be more damaging or persistent, as well as its relationship to sexual dimorphism in the brain. Thus, an early onset of BD may affect gonade-dependent neuromaturational changes to a greater extent than a later intake (Spear, 2015). Furthermore, it is necessary to characterise the neurocognitive anomalies prior to consumption with different levels of exploration, in order to identify decisive risk factors for BD and its perpetuation throughout adolescence. In order to do so, it is essential to use longitudinal designs that start before young people have started using substances.

Although the criteria for the inclusion/exclusion of participants in our studies have been truly comprehensive, it would be ideal to monitor the level of physical exercise of young people, especially if the research focuses on memory or related brain areas. Physical exercise not only favours hyppocampal neurogenesis and the cognitive functions dependent on this mechanism, but also appears to have important anti-inflammatory

properties (for a review Ryan and Nolan, 2016). In an animal model of BD rats, Maynard, and Leasure, (2013) showed that exercise was able to reverse hyppocampal damage caused by alcohol-intensive consumption by increasing brain natural self-repair processes. To our knowledge, only one neuropsychological study in young BDs has statistically controlled the effects of physical activity on cognitive performance (Salas-Gomez et al., 2016).

It would also of interest to investigate cognitive functions widely analysed in chronic alcoholism -but still unexplored in this population-, such as autobiographical memory, social cognition or emotional processing (Sullivan and Pfefferbaum, 2014). The use of new methods of analysis such as the study of functional connectivity is another line of progress with promising perspectives (Correas et al., 2016). In terms of novel lines of research, it would be interesting to delve into the potential "two-way interaction" between BD and sleep disturbances (Nguyen-Louie et al., 2017) and the dysregulation of the stress response (hypothalamic-hypothalamic–pituitary–adrenal axis) (de Timary et al., 2017).

Based on the above, a second approach would be the implementation of intervention and prevention programmes. Some preliminary studies have attempted to reduce heavy drinking in young people through cognitive training protocols that obtained an effective reduction in alcohol intake at least in the short term (the following week) (Black and Mullan, 2015; Houben, Wiers, Jansen, 2011; Houben, Havermans, Nederkoorn, Jansen, 2012). Interestingly, a recent study (Smith, Dashb, Johnstone, Houben and Field, 2017) highlights the importance of discerning between reducing alcohol consumption through participating in an alcohol-related study versus the specific effects derived from cognitive training. These authors

designed a study in which they tested the ability of a series of cognitive training protocols (inhibitory control) to reduce alcohol consumption, using a sample of regular drinkers and assigning them randomly to the control or the training condition. According to their results, the reduction in drinking levels the week after the study was due to simple participation in the study (cognitive training had no greater benefit than a task control). In short, more studies are needed in this area that use control conditions and repeated practice sessions over time to replicate the results in the long-term. Another innovative approach along these lines may be the application of non-invasive cortical stimulation techniques that appear to offer promising results in treating alcohol dependence, at least in terms of the likelihood of relapse and craving (da Silva et al., 2013; Klauss et al., 2014). Finally, the identification of a specific profile of risk factors (socio-demographic, neuroconitives, etc.) or subgroups with greater vulnerability could help to improve prevention strategies by refining the population target. This target-focused prevention should be implemented in combination with other measures that have proven to be effective such as increasing the price of alcoholic beverages, raising the minimum legal drinking age, implementing structural and environmental policies as well as educational programmes on university campuses (Elder et al., 2010; Foxcroft and Tsertsvadze, 2012; Wagenaar Salois, and Komro, 2009).

Ultimately, it should be noted that although BD is a phenomenon that peaks in late adolescence, a significant proportion of young people continue to maintain this pattern of consumption once adulthood has begun (ESTUDES, 2016). The inability to cease heavy use is likely to be associated with a number of concomitant problems (e.g. poor inhibitory control and alcohol bias), which in turn contribute to its clinical severity

(Carbia et al., 2018). It is therefore necessary to better understand the characteristics of this insufficiently investigated subgroup of young adults, applying the scheme of characterisation of pre-existing factors, as well as the cognitive anomalies derived from the prolonged use of BD. Thus, a pending challenge is to specify the factors that specifically define the subgroup of BDs that continue this practice into adulthood; therefore, maintaining an ethylic intake that alters and reprograms the development of the young brain (Kyzar, Floreani, Teppen and Pandey, 2016) making them, without a doubt, one of the most vulnerable subgroups to addiction.

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9

ANNEX

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ANNEX I:

Informed consent

UNIDADE DE NEUROPSICOLOXÍA E PSICOFISIOLOXÍA

Facultade de Psicoloxía

CONSENTIMENTO INFORMADO

D./Da. ..... declara que acepta ser avaliado para a investigación *"Consumo intensivo de alcohol (binge drinking) en xóvenes e adolescentes. Prevalencia e consecuencias neurocognitivas"*.

O propósito deste estudo é determinar as potenciais consecuencias neurocognitivas do consumo intensivo de alcohol en adolescentes e xóvenes. O estudo desenvólvese baixo a responsabilidade dos Dres. Caamaño, Cadaveira, Corral e Rgez. Holguín, da Universidade de Santiago de Compostela.

Toda a información de carácter persoal recabada no curso do estudo é confidencial, e non será revelada a ningunha persoa allea á investigación. Almacenarase en bases de datos cun número de identificación, non co nome das persoas. Os/as investigadores que, en razón da súa participación no estudo, teñen acceso á información, están suxeitos a segredo profesional.

O protocolo de avaliación completo consta de tres partes:

Entrevista: Tratará sobre cuestións relativas á historia psicolóxica e médica, incluíndo o uso de alcohol e outras drogas, rasgos de personalidade, estado de ánimo e estado cognitivo, así como cuestións relativas á historia de consumo de alcohol e drogas, así como a historia psicolóxica e médica de familiares biolóxicos próximos.

Avaliación neuropsicolóxica: Consiste na realización dunha serie de tests e probas, de tipo verbal e manipulativo, para a avaliación de diversas funcións cognitivas.

Avaliación psicofisiolóxica: Consiste no rexistro da actividade eléctrica cerebral, durante a realización dunha serie de sinxelas probas cognitivas. Esta avaliación faise mediante electroencefalografía, é dicir, mediante a colocación dun gorro de electrodos sobre a superficie da cabeza; utilízase un xel para mellorar o contacto entre os electrodos e a pel. Non é dorosa nin produce ningún tipo de efecto secundario. As únicas molestias derívanse da lixeira incomodidade que pode supor estar un certo tempo cos electrodos colocados, e con certa restrición de movementos, así como do feito de que poden quedar restos de xel no pelo que fan necesario lavar a cabeza despois da sesión.

Requírese do/a participante que colabore positivamente no estudo, respostando con veracidade e sinceridade ás preguntas formuladas na entrevista, e realizando as probas coa maior disposición.

Se algunha parte da avaliación lle resultara excesivamente fatigante, molesta ou estresante, o/a participante pode solicitar a súa suspensión, ou ben que se complete noutro momento; así mesmo, se algunha das preguntas realizadas na entrevista lle resulta dorosa ou moi incómoda de respostar, pode rexeitar facelo. Se o avaliador/a atopase indicios de calquera circunstancia que aconselle atención psicolóxica especializada, farallo saber ao/á participante.

Queda explícito que o/a participante pode decidir, en calquera momento, interrumpir a súa participación no estudo. Así mesmo, o equipo investigador pode tomar a decisión de excluílo/a.

A colaboración nesta investigación será gratificada con 5 € pola participación na fase de entrevista, e con 10 € pola participación nas avaliacións neuropsicolóxica e psicofisiolóxica (en conxunto por ambas as dúas).

A natureza do estudo e os procedementos a utilizar, así como a gratificación a recibir, foi explicada por .....

O/a participante recibe unha copia deste documento, que leu e entendeu, e acepta libremente participar neste estudo, baixo as condicións arriba descritas.

Data: ..... Sinatura:

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ANNEX II:

Authorization of the Bioethics Committee

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VICERREITORÍA DE INVESTIGACIÓN E INNOVACIÓN
Oficina de Investigación e Tecnoloxía
Servizo de Convocatorias e Recursos Humanos de I+S
Edificio CACTUS – Campus Vida
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Tel. 981 547 040 - Fax 981 547 077
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JOSÉ MANUEL CIFUENTES MARTÍNEZ, PRESIDENTE DEL COMITÉ DE BIOÉTICA DE LA UNIVERSIDAD DE SANTIAGO DE COMPOSTELA,

INFORMA:

Que el proyecto de investigación: **"Consumo intensivo de alcohol: caracterización de una nueva trayectoria hacia el alcoholismo"**, del que es Investigador principal el profesor D. **Fernando Cadaveira Mahía,** ha sido examinado por el Comité de Bioética de esta Universidad, cumpliendo su protocolo experimental los requisitos exigidos.

Este documento no exime de la obtención de permisos o autorizaciones y el cumplimiento de otras normativas de aplicación.

Lugo, 28 de julio de 2016.

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ANNEX III:

Neuropsychological tasks employed in each of the phases of the study

First evaluation	Second evaluation	Third evaluation	Fourth evaluation
D2	D2	Búsqueda de Símbolos (WAIS-III)	D2
Dígitos (WAIS-III)	Búsqueda de Símbolos (WAIS-III)	Clave de números (WAIS-III)	Clave de Números (WAIS-III=codificación)
Localización Espacial (WMS-III)	Clave de números (WAIS-III)	Dígitos (WAIS-III)	Dígitos (WAIS-III)
SOPT	Dígitos (WAIS-III)	Localización Espacial (WMS-III)	SOPT
Fluidez verbal (P/M/R y animales)	Localización Espacial (WMS-III)	SOPT	Mapa del Zoo (BADS)
WCST-64	SOPT	Fluidez verbal (F/A/S y Frutas -verduras)	AAVR (original)
Mapa del Zoo (BADS)	Fluidez verbal (P/M/R y animales)	WCST- F-C-N /D2	Memoria Lógica, Textos (WMS-III)
Búsqueda de llaves (BADS)	WCST-64	Mapa del Zoo (BADS)	Test de los seis elementos modificado
IGT	Mapa del Zoo (BADS)	Búsqueda de llaves (BADS)	Five Digit Test (FDT)
AAVR	Búsqueda de llaves (BADS)	IGT	Vocabulario (WAIS-III)
Memoria Lógica, Textos (WMS-III)	IGT	AAVR	
Escenas (WMS-III)	AAVR	Memoria Lógica, Textos (WMS-III)	
Vocabulario (WAIS-III)	Memoria Lógica, Textos (WMS-III)	Escenas (WMS-III)	
	Escenas (WMS-III)	Vocabulario (WAIS-III)	
	Vocabulario (WAIS-III)		

Nota. AAVR=Aprendizaje Auditivo Verbal de Rey; SOPT= Self Ordered Pointing Test; WCST=Test de Clasificación de Tarjetas de Wisconsin; IGT= Iowa Gambling Task; BADS= Behavioral Assessment of Dysexecutive Syndrome.

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ANNEX IV:

Authorization of co-authors

Don/a……

con enderezo en...

Teléfono……mail……..

MANIFESTO QUE:

Como coautor/a DOUTOR/A dos artigos integrados na tese que presenta

Dona Carina Carbia Sinde

quedo informado/a de que ten solicitada autorización da CAPD da USC para a presentación do exemplar da súa tese en formato de compendio de publicacións e polo tanto autorizo a inclusión dos artigos dos que formo parte como coautor/a RENUNCIANDO á presentación dos traballos relacionados como parte da miña tese de doutoramento.

Carbia, C., López-Caneda, E., Corral, M., Cadaveira, F. (2018). A systematic review of neuropsychological studies involving young binge drinkers. Neuroscience & Biobehavioral Reviews. (*in press*) DOI:10.1016/j.neubiorev.2018.04.013

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Santiago de Compostela a 2 de, Maio de 2018.

Asinado (sinatura orixinal)