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Brain magnetic activity profiles of young binge drinkers

Perfiles de actividad magnética cerebral de jóvenes con consumo intensivo de alcohol

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María Ángeles Correas Marín

Director

Fernando Maestú Unturbe

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Tesis doctoral de

María Ángeles Correas Marín

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INDEX

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LIST OF PUBLICATIONS

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Experimental Study II

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Experimental Study III

Correas A., Beaton L., López-Caneda E., Rodriguez Holguín S., García-Moreno L.M., Cadaveira F., Maestú F., Marinkovic K. (2016). Oscillatory spatial profile of young binge drinkers during a Go/NoGo task. *(In process)*

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GLOSSARY

ACC	Anterior Cingulate Cortex
AC	Amplitude Correlation
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
ANOVA	Analysis of Variance
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood Alcohol Concentration
BD	Binge Drinking
BOLD	Blood-Oxygen-Level Dependent
BIS	Barrat Impulsivity Scale
CNS	Central Nervous System
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Image
EC	Effective Connectivity
EC	Eyes Closed
EEG	Electroencephalography
EO	Eyes Open
ERF	Event Related Field
ERP	Event Related Potential
FC	Functional Connectivity
FMC	Frontal Medial Cortex
fMRI	Functional Magnetic Resonance Image
$GABA_A$	Gamma-aminobutyric-A acid
GNG	Go-NoGo task
iEEG	Intracranial Electroencephalography
IPL	Inferior Parietal Lobe
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
NDSS-S	Nicotine Dependence Scale
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NMDA	N-methyl-D-aspartate
Pc	Precuneus
PCC	Posterior Cingulate Cortex
PET	Positron Emission Topography
PFC	Prefrontal Cortex
PMBR	Post-movement Beta Rebound
PLV	Phase Locking Value
PS	Power Spectrum
ROI	Region of Interest
SC	Structural Connectivity
STFT	Short Time Fourier Transform
SUD	Standard Unit Drink
SQUID	Superconducting Quantum Interference Device
TFR	Time Frequency Response

LIST OF FIGURES

LIST OF TABLES

RESUMEN

El patrón de consumo de alcohol *binge drinking* se caracteriza por la ingesta intermitente de grandes cantidades del alcohol en un corto espacio de tiempo alternándose con periodos de abstinencia. En España, este tipo de consumo de alcohol se asocia al conocido *efecto botellón* en el que los jóvenes se reúnen en espacios públicos, principalmente los fines de semana, teniendo el alcohol como protagonista. La adolescencia, edad en la que se inicia este tipo de consumo, es considerada un periodo crítico de desarrollo en el que el cerebro experimenta grandes cambios madurativos, fundamentalmente en los lóbulos frontales. Dada su inmadurez, el cerebro adolescente muestra mayor vulnerabilidad ante el efecto neurotóxico del alcohol que el cerebro adulto. Debido a la alta prevalencia que este tipo de consumo presenta entre los jóvenes, la comunidad científica ha mostrado interés en las últimas décadas por estudiar las posibles consecuencias que puede tener en la estructura y funcionamiento del cerebro de jóvenes que beben de este modo. Sin embargo, hasta el momento no existían estudios que evaluasen el efecto del *binge drinking* en la actividad magnética cerebral.

La Magnetoencefalografía es una técnica no invasiva que mide las corrientes magnéticas generadas por las pequeñas corrientes neurales que producen las neuronas. La presente tesis ha utilizado esta técnica a lo largo de los tres experimentos en los que se estudió: 1) la actividad magnética cerebral en el espacio de los sensores asociada del estado de reposo de jóvenes universitarios de 18-19 años con el patrón *binge drinking* y un grupo control, 2) la actividad magnética cerebral en espacio de las fuentes del estado de reposo y la conectividad estructural de los mismos jóvenes dos años más tarde, con 20-21 años; y 3) la actividad magnética cerebral en espacio de las fuentes asociada a una tarea Go/NoGo de los mismos jóvenes durante la primera fase del estudio, cuando tenían 18-19 años.

Los resultados del primer estudio mostraron que tanto la conectividad funcional como la potencia espectral, durante un estado de reposo con ojos cerrados, diferían entre grupos. El estudio estadístico indicó que 1) el grupo *binge drinking* mostraba un decremento de potencia en la banda alfa y un incremento en las banda teta; 2) la conectividad funcional estaba incrementada in el grupo experimental en las bandas delta, teta y beta; y decrementada en la banda alfa, comparado con el grupo control. Además, esta disminución de la conectividad funcional del grupo *binge drinking* correlacionó negativamente con la concentración de alcohol en sangre estimada, apoyando la idea de que las diferencias psicofisiológicas encontradas están relacionadas con la cantidad de alcohol ingerida.

En el segundo estudio, los resultados muestran que la conectividad funcional entre los links de la Default Mode Network incrementa a lo largo del tiempo en los sujetos que persistieron en el consumo de alcohol a lo largo de los dos años de seguimiento. Por otro lado, la conectividad estructural medida mediante la anisotropía fraccional, difusividad media, radial y axial no reveló diferencias entre grupos ni a lo largo del tiempo. Estos resultados mostraron que el mantenimiento del patrón de consumo *binge drinking* conlleva a un incremento anómalo de la conectividad funcional en el proceso de maduración normal, incluso antes que se detecten cambios a nivel estructural.

Por último, respecto al estudio con la tarea Go/NoGo equiprobable, los resultados mostraron que a pesar de que ambos grupos alcanzaron un nivel de ejecución similar en la tarea cognitiva, a nivel psicofisiológico sí aparecieron diferencias entre grupos. El análisis estadístico indicó que 1) en la banda de frecuencia teta, la potencia la evocada por el estímulo Go fue significativamente inferior en el grupo binge drinking en el área motora izquierdo y las áreas bilaterales del córtex prefrontal ventrolateral. Además, el estudio de correlaciones mostró que la potencia en estas áreas correlacionaba positivamente con el rendimiento en la tarea Go/NoGo y con la del test de atención D2. Asimismo, el potencia en teta también correlacionó negativamente con la estimación del volumen de alcohol en sangre en un episodio *binge drinking* habitual y con rasgos de impulsividad auto-reportada. 2) En la banda de frecuencia beta, la potencia la evocada por el estímulo Go también fue menor en el grupo binge drinking que en el grupo control en el área derecha del córtex prefrontal ventrolateral. En conjunto, estos resultados indican que el patrón de consumo *binge drinking* está asociado con un déficit de activación en las bandas teta y beta durante la detección de estímulos. Además, las correlaciones parecen indicar que el déficit en los recursos atencionales (D2) podría ser una causa subyacente a las diferencias psicofisiológicas encontradas. Por otro lado, las correlaciones con la estimación del nivel de intoxicación alcohólica y con los rasgos de impulsividad apoyan la idea de que estos déficits psicofisiológicos en el grupo *binge drinking* pueden ser consecuencia del consumo de altos niveles de alcohol que adicionalmente podrían estar modulados por rasgos de impulsividad.

En conclusión, los tres experimentos de la presente tesis confirman la existencia de diferencias psicofisiológicas asociadas al consumo intensivo del alcohol durante la adolescencia. En el caso de la actividad magnética cerebral durante el estado de reposo, estas diferencias parecen estar presentes tanto durante los primeros años de universidad como en los consecutivos entre los sujetos que persistían con ese consumo. En el caso de la tarea cognitiva, los déficits encontrados en los sujetos bebedores parecen estar relacionados con déficits subyacentes en procesos

atencionales y de control inhibitorio. A pesar de no poder establecer una dependencia causal entre las diferencias psicofisiológicas y el consumo de alcohol, podemos establecer su relación y con ello confirmamos la vulnerabilidad que el cerebro adolescente presenta frente al consumo intensivo de alcohol. Además, estas diferencias encontradas podrían representar un signo inicial de actividad cerebral anómala asociada al consumo de alcohol. La alta prevalencia del *binge drinking* este consumo entre jóvenes pone de manifiesto la necesidad de futuros estudios con el fin de clarificar la dimensión de las consecuencias de este consumo en la salud.

ABSTRACT

The alcohol consumption binge drinking pattern is characterized by intermittent intake of large amounts of alcohol in a short space of time, alternated with periods of abstinence. In Spain, this type of alcohol consumption is associated with the well-known *"efecto botellón"* where young people gather in public spaces, especially on weekends, having the alcohol as the protagonist. Adolescence, the age in which this type of consumption begins, is considered a critical period of neural development in which the brain undergoes maturational changes, mainly in the frontal lobes. Given its immaturity, adolescent brain is more vulnerable to the neurotoxic effects of alcohol than the adult brain. Because of its high prevalence among young adolescents, since last decades the scientific community has shown increasing interest to study the possible consequences that *binge drinking* may have on the structure and functioning of the brain. However, so far there are no studies assessing the effect of binge drinking with Magnetoencephalography.

Magnetoencephalography is a noninvasive technique that measures the magnetic currents generated by neural currents produced by pyramidal neurons. The present dissertation has used this technique over the three experiments, studying: 1) brain magnetic activity in the sensor space associated to resting state of university students of aged 18-19 years old with alcohol binge drinking pattern and also a control group, 2) brain magnetic activity in the source space also associated to resting state and structural connectivity of the same young students two years later, with 20-21 years old; and finally, 3) the brain magnetic activity in source space associated with a Go/NoGo task in the first phase of the study, when the participants were 18-19.

The results of the first study showed that both functional connectivity and spectral power during resting state differed between groups. The statistical study indicated that: 1) the binge drinking group showed a decrease of power in the alpha band and an increase in the theta band; 2) functional connectivity was increased in the experimental group in delta, theta and beta bands; and decremented in the alpha band, compared with the control group. In addition, this decreased functional connectivity in the alpha band negatively correlated with the blood alcohol concentration estimated for a typical binge drinking episode, supporting the idea that the psychophysiological differences found are related to the amount of ingested alcohol.

In the second study, the results showed that the functional connectivity between the Default Mode Network links increases over time in subjects who persisted in alcohol consumption over the two years follow-up. Furthermore, structural connectivity measured by fractional anisotropy,

mean, radial and axial diffusivity revealed no differences between groups or over time. These results showed that maintaining the consumption pattern of alcohol binge drinking leads to an abnormal increase in functional connectivity along the normal maturation process, even before changes are detected at the structural level.

Finally, regarding the Go/NoGo task study, the results showed that although both groups reached a similar level of performance in cognitive task (Go/NoGo), at a physiological level there were differences between groups. The statistical analysis indicated that 1) in theta frequency band; power evoked by Go stimuli was significantly lower in the binge drinking group in the left motor area and the bilateral ventrolateral prefrontal cortex areas. In addition, the study showed that power correlations in these areas correlated positively with performance on the task and also with the D2 attentional test. Besides, theta power negatively correlated with the estimated blood alcohol concentration estimated and with self-reported impulsivity traits (BIS). 2) In the beta frequency band, power evoked by Go stimulation was also lower in the binge drinking group that in the control group in the right ventrolateral prefrontal cortex area. Together, these results indicate that binge drinking consumption is associated with a deficit in theta and beta activation during stimuli detection. In addition, correlations suggest that the deficit in attentional resources (D2) could be an underlying cause of the psychophysiological differences. On the other hand, correlations with the estimated blood alcohol concentration and with impulsivity traits support the idea that these psychophysiological deficits in binge drinkers may be result of consuming high levels of alcohol and, additionally, could be modulated by impulsivity traits.

In conclusion, the three experiments confirm the existence of psychophysiological differences associated with heavy alcohol consumption during adolescence. In the case of the brain magnetic activity during resting state, the differences between groups appear to be present at the first year of university and also the consecutive years among those subjects who persisted with that pattern consumption. In the case of the cognitive task, deficits found in drinkers appear to be associated with underlying deficits in attentional and inhibitory control processes. Despite being unable to establish a causal dependency between psychophysiological differences and alcohol consumption, we can establish their relationship and thus confirm the vulnerability that adolescent brain presents to the intensive consumption of alcohol. Moreover, these differences found could represent and early sign of abnormal brain activity associated with alcohol consumption. The high prevalence of binge drinking among young adolescents highlights the need for future studies to clarify the extent of the consequences on health.

1. GENERAL INTRODUCTION

1.1. Alcohol

Alcoholic beverages are a widespread product in Western culture and highly valued socially. Ethanol, like other drugs, has great addictive quality but, unlike with most of them, it is also possible to consume alcohol (in moderate amounts) without adverse health consequences or dependence; that is the main reasons why alcohol consumption is very socially tolerated. Despite the fact that most consumers do not meet alcohol abuse or dependence criteria, in population terms, the impact that alcohol has at health, social and economic level is remarkable (Eurobarometer, 2010; Substance Abuse and Mental Health Services Administration, 2013a). As a consequence of that, alcohol-related problems are one of the most studied addictive disorders.

1.1.1. Metabolism

Ethanol absorption after oral alcohol consumption occurs in the digestive tract, largely in the small intestine. Ethanol absorption rate determines the magnitude of its blood concentration, the intensity and duration of its pharmacological effects. Ethanol molecule dissolves better in water than in lipid; therefore, its distribution is analogous to the distribution of water in the body. Furthermore, ethanol crosses, without difficulty, the placental barrier and the blood-brain barrier (Aragón, Miquel, Correa, & Sanchis-Segura, 2002).

Ethanol metabolic degradation is mainly produced by hepatic oxidation and mediated by alcohol dehydrogenase enzyme (ADH); becoming acetaldehyde, a highly toxic substance and responsible of the aversive effects of alcohol. In a second step, the acetaldehyde produced is metabolized down to acetate via aldehyde dehydrogenase (ALDH). Then, acetate is broken down into water and carbon dioxide for easy elimination. Also, 2-5% of the ethanol clearance is associated with non-metabolic factors and is eliminated without suffering any transformation, through its incorporation into the urine, feces, sweat and exhaled air (Lands, 1998). See figure 1-1.

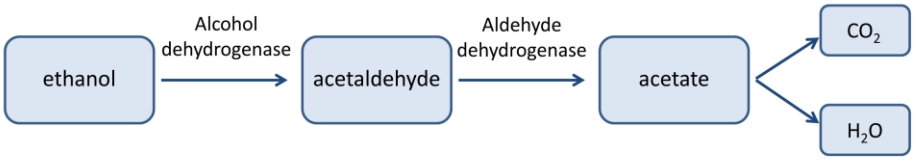

Figure 1-1 Schematic representation of alcohol metabolism

It is worth mentioning that there are differences in alcohol metabolism between genders. These differences cause that women, with the same amount of alcohol consumption, achieve higher blood alcohol concentration (BAC) than men and therefore more acute intoxication. This is basically explained by two factors: 1) the lower activity of the ALDH and 2) a smaller amount of water in the female body that facilitates greater rate of absorption of ethanol.

Alcohol metabolism rate is constant, about 15 ml per hour, regardless of the amount or the speed of alcohol consumption. Indeed, alcohol is metabolized slower than is absorbed, therefore, when the intake of alcohol beverages is fast, the liver cannot metabolize so quickly and acetaldehyde accumulates causing alcohol intoxication.

1.1.2. Effects on brain neurotransmission systems

In general, the effects of ethanol intoxication follow a biphasic time course as the initial feelings of relaxation and exuberance might give way to hangover, exhaustion, depression or even vomiting and loss of consciousness in cases of higher doses.

Alcohol affects brain function by interacting with multiple neurotransmitter systems, thereby disrupting the delicate balance between inhibitory and excitatory neurotransmitters by means of the interaction of two specific receptors: gamma-aminobutyric-A acid ($GABA_A$) and N-methyl-D-aspartate (NMDA) of glutamate (see figure 1-2).

Short term alcohol consumption acts as a depressant of the central nervous system (CNS) increasing the inhibitory neurotransmission, especially potentiating the action of $GABA_A$ which is the major inhibitory neurotransmitter in the CNS and, on the other hand, decreasing excitatory neurotransmission by inhibiting the action of the glutamate, the main excitatory neurotransmitter in the CNS (Valenzuela, 1997).

During alcohol intoxication, the potentiation of GABA´s inhibitory action, especially in the Purkinje cells of the cerebellum responsible for the body position in space and motor coordination, is

considered responsible for the alcohol intoxication cerebellar symptoms as motor incoordination. In addition, the NMDA receptors blocking appears to be responsible, among others, for the transient memory loss occurring during alcohol intoxication (Izquierdo, 2002).

Moreover, alcohol, like other drugs, also causes dopamine release in the mesolimbic system, resulting in euphoria and the subjective experience of pleasure associated with the process of addiction (Mitchell et al., 2012; Wise, 1998).

However, after long-term alcohol exposure, the brain attempts to compensate by tilting the balance back toward equilibrium by compensating for the depressant effects of alcohol; thus the brain decreases inhibitory neurotransmission and enhances excitatory neurotransmission. These neural changes occur as the development of tolerance to alcohol´s effects. When alcohol consumption is abruptly discontinued or reduced, these compensatory changes are no longer opposed by the presence of alcohol, thereby leading to the excitation of neurotransmitter systems and the development of alcohol withdrawal syndrome.

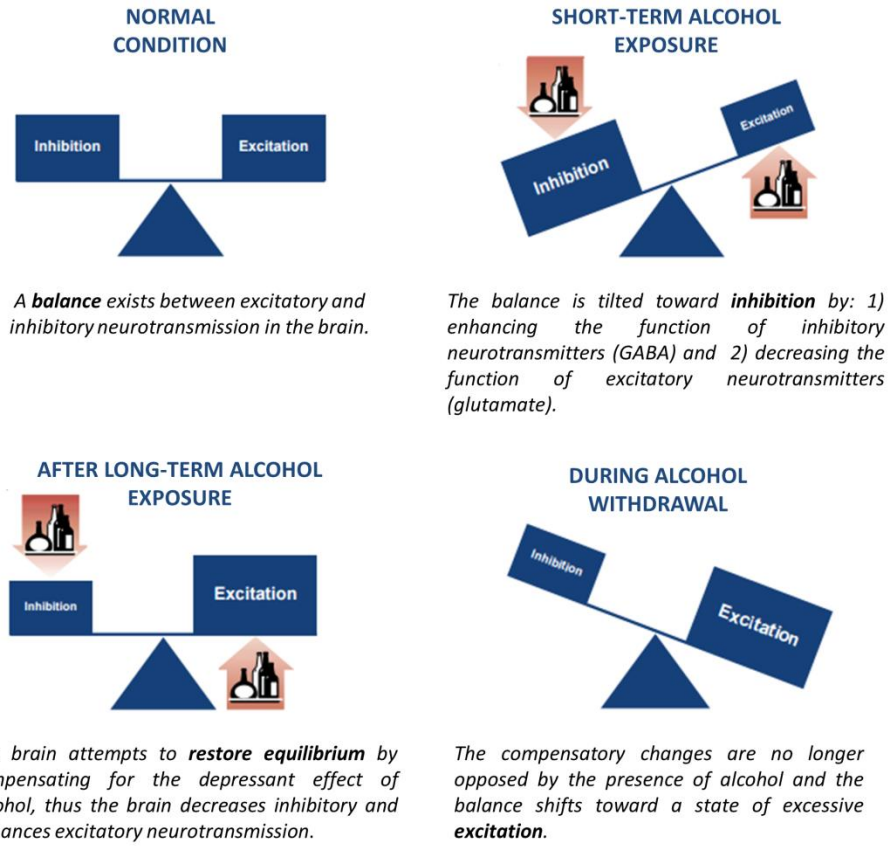

Figure 1-2 Alcohol´s effects in the neurotransmitter system.
Schematic representation of alcohol´s effects on the balance of inhibitory and excitatory neurotransmission in the brain. (Valenzuela, 1997)

Therefore, although a single massive intake of alcohol may have dramatic acute consequences (e.g., increased risk of vehicle collisions, alcoholic coma, and uninhibited sexual or violent behavior), repeated alcohol intake over a long period leads to negative long-term medical (e.g., cardiovascular and gastrointestinal disorders). In fact, it is well established the neurotoxicity - induced by long-term chronic alcoholism (Harper, 2009). Several decades of research in adults have shown that chronic alcohol abuse is associated with brain and cognitive impairments (Harper, 2009; Oscar-Berman & Marinković, 2007). However, the consequences caused by massive consumption of alcohol during adolescence and youth are still scarcely investigated and they will be studied throughout this dissertation.

1.2. Adolescence and alcohol

Adolescence is the transition between childhood and adulthood. This critical period of development is characterized by a wide range of neuronal, emotional and behavioral changes. Reaching adolescence involves seeking new experiences, greater exposure to risks and seeking social acceptance, all behaviors related with alcohol or other drugs consumption. This is the main reason why adolescence is the principal stage in which many young people start their use of psychoactive substances as alcohol. As discussed below, the neuronmaturational changes occurring during this period, involve a specific vulnerability of the adolescent brain to the neurotoxic effects of alcohol.

1.2.1. Brain development and alcohol

The brain development that occurs along this period is characterized by ordered changes, such as, synaptic pruning and brain myelination that lead to the maturation of functional (Sherman et al., 2014) and structural networks (Simmonds, Hallquist, Asato, & Luna, 2014), supporting cognitive development at this age. First, the *synaptic pruning* makes reference to the elimination of certain connections underused while strengthening those most commonly used connections. Pruning starts near the time of birth and is completed by the time of sexual maturation. This process is associated with an improvement in communication between neural networks, making the synaptic circuits more efficient (Casey, Galvan, & Hare, 2005).

The other neuromaturational process that occurs during adolescence and early adult stage is the *myelination (or myelinogenesis)*. The formation of myelin sheaths that surround the axons causes an increase in the speed of conduction of action potentials and, therefore, the transmission rate of neural information. In humans, myelination begins in the 14th week of fetal development and continues through the adolescent stage of life. Given that this increase in white matter follows a postero-anterior course, the frontal lobes are the latest to complete its full maturation (Blakemore & Choudhury, 2006). Accordingly to this myelination progression, from an anatomical point of view, the cerebral region experiencing the most notable changes during adolescence is the prefrontal cortex (Lenroot & Giedd, 2006). This maturation in frontal regions has special relevance because this area is the responsible of the refinement of higher-order executive functions (Spear, 2000). Supporting this fact, several studies have shown that as the prefrontal cortex (PFC) develops, the performance of higher order cognitive functions such as inhibitory control, working

memory or decision making, improves (Hooper, Luciana, Conklin, & Yarger, 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Tamm, Menon, & Reiss, 2002).

The immaturity in these cognitive processes that characterize the adolescence explains why this stage is a time of exploration and limit testing and, therefore, the chief period for initiating substance use, which can lead to the development of later alcohol or drug use disorders (Zeigler et al., 2005). For example, in the case of alcohol consumption, it is known that early onset of binge drinking or exposure to binging has been linked to the increased risk of drinking heavily in adulthood (Wechsler, Dowdall, Davenport, & Castillo, 1995).

1.2.2. Inhibitory control & alcohol consumption: a circular problem

Within the various cognitive functions that could be related with to alcohol consumption, the inhibitory control deserves particular consideration (for a review see (E López-Caneda, Rodríguez Holguín, Cadaveira, Corral, & Doallo, 2013). As stated above, the inhibitory control, like the rest of the executive functions, progressively improves with age from infancy to young adulthood, when it becomes more efficient (Luna, Padmanabhan, & O'Hearn, 2010; Tamm et al., 2002).

Inhibitory control is a fundamental component of human behavior. Behavioral inhibition has been defined as the ability to suppress responses that are ready to be emitted (proponent responses) and it comprise the motor inhibition measured with a Go/NoGo task (GNG). During a GNG task stimuli are presented in a continuous stream and participants perform a binary decision on each stimulus. Go stimuli require participants to make a motor response (Go) whereas the NoGo requires participants to withhold the response. Go stimulus usually has greater frequency than the NoGo and therefore their response is proponent, so motor control inhibition is required to refrain the answering to NoGo stimulus. In relation to alcohol, it is considered that the effective capability to inhibit an action may prevent alcohol misuse, on the contrary, it is known that ineffective response inhibition may promote more vulnerable to develop addictive behaviors (Perry & Carroll, 2008).

The immaturity inhibitory control ability during adolescence appears to be linked to the peak onset of substance abuse observed through this period (Steinberg, 2008). In fact, numerous studies have associated a weak inhibitory control with alcohol use during adolescence and youth (Henges & Marczinski, 2012; Nigg et al., 2006; Rubio et al., 2008). Studies of subjects with family history of alcohol use disorders have shown a lower response in the inhibition performance in this population (Nigg et al., 2004; Alecia D Schweinsburg et al., 2004) as well as anomalies in the anatomical and functional structure of some regions involved in inhibitory control (Heitzeg, Nigg,

Yau, Zucker, & Zubieta, 2010; Hill et al., 2009; Alecia D Schweinsburg et al., 2004). In the line with this findings, several authors have proposed weak inhibitory control as a general vulnerability factor for addictive behaviors, including alcohol use disorder (Brewer & Potenza, 2008; Goldstein & Volkow, 2002, 2011).

But, it is known that the inhibitory control plays a dual role in the relation with alcohol consumption. On one hand, reduced inhibitory control ability previous to any consumption may play an important role in the initiation of drinking and the development of alcohol misuse; and on the other hand, a deficit of the inhibitory control can be caused by heavy alcohol consumption.

In this line, studies have found that adolescents and youths under acute effects of alcohol exhibit poor performance in tasks measuring inhibitory control (Ostling & Fillmore, 2010). And, in addition to the effects that alcohol has in the inhibitory control, studies about *binge drinking* (BD) have associated this type of alcohol consumption among young drinkers with abnormalities in brain function and behavioral performance related to response inhibition (Nederkoorn, Baltus, Guerrieri, & Wiers, 2009b; Scaife & Duka, 2009; Townshend & Duka, 2005). As López-Caneda et al. pointed out (E López-Caneda et al., 2013), heavy alcohol consumption during the adolescence might lead to a "snowball effect" by which the acute effects of alcohol on prefrontal lobs and especially on the inhibitory control ability would promote a continuous auto-administration of alcohol and keep contributing to the deterioration of the inhibitory control.

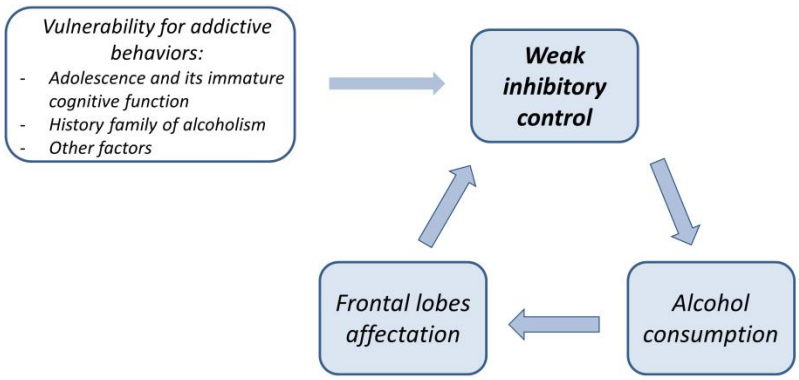

Figure 1-3 Alcohol consumption, adolescence and inhibitory control

In conclusion, it is considered that there are two ways in which alcohol is related with inhibitory control in the adolescence. First, adolescence is characterized by a weak inhibitory control due to the immaturity of the brain circuitry supporting this executive function. This reduced inhibitory control ability consequently may affect the ability to control the alcohol intake. Secondly, drinking

alcohol heavily during adolescence and youth, in turn, may entail a weakening of the inhibitory control, leading to a lower ability to stop alcohol consumption.

At this point, it is important to consider that the cross-sectional nature of studies exploring neurocognitive functioning in young and adolescent binge drinkers makes it difficult to draw a conclusion about causal relationships. Thus, longitudinal studies are needed to evaluate the extent of the interaction between the inhibitory control dysfunction and alcohol use in both directions: as a vulnerability factor and also as an effect of excessive drinking at this age.

1.2.3. Alcohol effects on the adolescent brain: Animal Studies

Last decade, several animal studies have shown that indeed the adolescent brain, still immature and in a critical period of remodeling and development, is particularly sensitive to the harmful effects of alcohol consumption.

Crews and cols. found that alcohol induces more brain damage in adolescent than in adult rats exposed to equal high levels of alcohol, especially in regions of the orbitofrontal and temporal cortex (F T Crews, Braun, Hoplight, Switzer, & Knapp, 2000). Besides the prefrontal cortex, the hippocampus seems to be also vulnerable to alcohol consumption during adolescence. Swartzewelder and cols. found that the young brain is particularly vulnerable to alcohol blocking of NMDA receptors in the hippocampus. Therefore, synaptic plasticity in the hippocampus associated with memory is attenuated by alcohol in a greater extent in adolescent rats than adult rats (White & Swartzwelder, 2004).

Moreover, another study conducted with primates, showed that the ingestion of large amounts of alcohol affects neuronal development processes that occur during adolescence in the hippocampus (Taffe et al., 2010). The authors observed that the group of primates exposed to alcohol had increased neural degeneration in the hippocampus due to non-apoptotic process. Taffe et cols. interpreted this data as the basis of cognitive deficits in learning and memory task related to hippocampal function observed in alcoholics.

At a neurocognitive level, rodent models also have revealed higher degree of cognitive impairment in adolescents rats exposed to alcohol than in adult rats exposed to the same level of alcohol (Barron et al., 2005; Markwiese, Acheson, Levin, Wilson, & Swartzwelder, 1998; Sircar & Sircar, 2005).

1.3. Binge drinking

Although alcohol consumption in Spain has been strongly linked to gastronomy and culture, during the last decades this practice has been modified, especially among young people. At the present time, a new pattern of alcohol consumption has gained popularity among adolescent and in Spain has been linked with the *"botellón"* effect. This pattern is characterized by the intake of large amounts of alcohol in a short period of time and alternating it with periods of abstinence between drinking episodes (Courtney & Polich, 2009; Parada, Corral, Caamaño-Isorna, Mota, Crego, Rodríguez Holguín, et al., 2011). The large social tolerance to alcohol consumption along with the low perception of risk associated to this practice has been major factors in the spread among young people of intensive alcohol consumption.

The concern that has acquired this new pattern of consumption is due to the social and health consequences associated with it (traffic accidents, assaults, and poor academic performance and alcohol health problems related) (Goslawski et al., 2013; Mota et al., 2010; Svensson & Landberg; Valencia-Martín, Galán, & Rodríguez-Artalejo, 2008) as well as the high prevalence that have among young people and adolescents in most Western countries (Substance Abuse and Mental Health Services Administration, 2013b; Toxicomanías, 2012).

Definition of Binge Drinking

The expression of "binge drinking" has engendered a wide collection of definitional elements since its conception. In order to obtain a multidimensional definition we have to consider both *quantity* and *frequency* of consumption as defining characteristics of binge drinking.

Although numerous definitions proposed so far have taken into account these variables, there is no comprehensive agreement on the definition.

Quantity: in the 90´s, Wechsler et al., in the *Harvard School of Public Health College Alcohol Study,* from an initial view defined *binge drinking* as the consumption of five drinks or more for men and four drinks or more for woman on a single occasion within the past 2 weeks (Wechsler, Davenport, Dowdall, Moeykens, & Castillo, 1994). The adjustment to the four-drink cutoff for women was based on their lower rate of gastric metabolism for alcohol which leads to higher blood alcohol levels compared with men for the same quantity (Wechsler et al., 1995).

Although currently Wechsler´s proposal is fairly widespread, there is some controversy around it. The main limitation is primarily focused on the lack of definition of a Standard Unit Drink (SUD).

The alcohol grams present in a SUD varies from country to country (see Table 1-1) and therefore, these differences make it necessary to adapt the criteria to the country in which the study is being carried out. In the case of Spain, the standard considers that a SUD equals 10 grams of pure ethanol (Parada, Corral, Caamaño-Isorna, Mota, Crego, Rodríguez Holguín, et al., 2011).

Table 1-1 Grams of a Standard Unit Drinking per country. (ICAP, 2003)

Country	Gr of alcohol/SUD
United Kingdom	8
Netherlands	9,9
Australia, Austria, Ireland, New Zealand, Poland and Spain	10
Finland	11
Denmark, France, Italy and South Africa	12
Canada	13,6
Portugal, USA	14
Japan	19,75

One attempt to determine more precisely what the appropriate threshold for establishing a pattern BD is using the blood alcohol concentration (BAC) level. Using this concept, a standardized conceptual definition of binge drinking was proposed by the *National Institute on Alcohol Abuse and Alcoholism* (NIAAA) in 2004: "Binge is a pattern of drinking alcohol that brings BAC to 0.08 gram % or above. For the typical adult, this pattern corresponds to consuming five or more drinks (male), or four or more drinks (female) in about two hours" (National Institute of Alcohol and Alcoholism, 2004). Thus, considering that in Spain one SUD equals 10 grams of pure ethanol, a better approximation to the NIAAA criteria would be the consumption of 6 SUD (60 gr) or more for men and 5 (50 gr) or more for women in an interval of approximately of 2 hours, a consumption that results in BAC of 0.08 gram %.

The definition does not specify, however, the time period or number of binging occurrences that would describe a long-term binge-drinking practice. Thus, NIAAA´s definition characterizes single binge episodes but does not capture the consumption pattern associated with serious health social consequences.

Time-frame (frequency): the inclusion of a past time-frame to quantify frequency of binging episodes is necessary to differentiate "binge drinking" from "alcohol dependence". Although there is no uniform approach to characterize the BD pattern in terms of *frequency*, the most widespread and currently accepted (and used in the experiments of the present thesis) is when the binge episode occurred at least once within the past month.

Definitions also refer to the *duration of the drinking session*, usually considering the intake of 60/40 grams of alcohol in a two-hour interval what results in a BAC of 0.08 gram % or above (National Institute of Alcohol and Alcoholism, 2004).

Finally, another important aspect to define the BD pattern is the instrument used to collect the data and select the BDs participants. For this purpose, different self-administered questionnaires are usually used, including the *daily consumption* (Rehm, 1998), the Alcohol Use Disorders Identification Test (AUDIT) (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) or the Alcohol Use Questionnaire (Mehrabian & Russell, 1978). But it can also be asked within a semi-structured interview about the amount and frequency variables of alcohol consumption. All these instruments have shown a good concordance index, however the AUDIT seems to be the best identifying BD (Shakeshaft, Bowman, & Sanson-Fisher, 1998).

Taken together, when studying BD in young population, it is needed to consider different aspects such as quantity, frequency, speed of consumption and tools used to collect the data. The combination of all these variables, as well as the adaption to the country where the study is carried out, makes it difficult to establish a unanimous operative definition of BD.

Epidemiology

According to several national and international epidemiological reports, the proportion of adolescents and young people (especially university students) that has a BD pattern has increased in the last decade.

The majority of epidemiological studies have been conducted in the USA and northern Europe because in these two regions there is a higher rate of sporadic alcohol consumption associated with drunkenness. Conversely, in the countries of southern Europe (specially on the Mediterranean coast), alcohol consumption is more regular and linked to gastronomic culture (Bloomfield, Stockwell, Gmel, & Rehn, 2003). Although Mediterranean countries traditionally have more distributed alcohol consumption (less massive consumption as in the northern Europe), several studies have highlighted the change in consumer habits that has occurred among young people in these countries. Thus, currently these countries show increased intermittent alcohol consumption, usually focused on the weekends, with preference for high alcohol content beverage, higher drinking speed and low concern of the risk (Bloomfield et al., 2003; D'Alessio, Baiocco, & Laghi, 2006; Delegación del gobierno para el Plan Nacional sobre Drogas, 2015).

In the United States, 21% of youth acknowledge having had "*more than a sip"* of alcohol before 13 years of age and most (79%) have done so by 17 years old. Besides, among youth who drink,

the proportion that drinks heavily is higher than among adult drinkers, rising from approximately 50% in those of 12-14 years of age, to 72% among those form 18-20 years old (Siqueira & Smith, 2015).

In Europe, the last *Eurobarometer* report: *EU citizens´ attitudes towards alcohol* showed that 43% of young people have had a binge drinking episode at least once in the last month. Moreover, this consumption appears to be more prevalent in younger age groups (Eurobarometer, 2010).

In Spain, the 18% of the population aged 15 to 34 consume alcohol with a binge drinking pattern and the average age of the first use of alcohol is 16,8 years old (Parada, Corral, Caamaño-Isorna, Mota, Crego, Rodríguez Holguín, et al., 2011). In fact, Spain ranks fifth in Europe in number of BDs (34% of those aged 15 to 24 years), five points above the average of the European Union (24%).

Taken together, despite of the variability between epidemiological studies on the prevalence of BD, the studies show a clear presence of this pattern of alcohol consumption among adolescents and university students in Spain as well as in other Western countries. This increase in the prevalence of alcohol intake among young people in several Western justifies the interest in the present dissertation of studying the possible cerebral consequences that this consumption can have on BD population.

1.3.1. Binge drinking and Neuropsychological studies

Since the last decades, there have appeared several studies assessing the neuropsychological effects of BD during adolescence. The cognitive functions that have been found associated to BD consumption are attention, memory and mainly, executive functions. For a revision see (Eduardo López-Caneda, Mota, et al., 2014).

Different studies assessing attention agree to note differences in performance between the control and BD groups in different subtypes of attention. Regarding focused attention, young BDs showed lower performance in tasks of auditory and visual attentional *span* (Sanhueza, García-Moreno, & Expósito, 2011). Moreover, BD population also showed worse performance with a sustained attention task (Hartley, Elsabagh, & File, 2004) and, just in the BD woman group, with a monitoring task (Townshend & Duka, 2005).

The studies on memory and BD have been divided into verbal and visual declarative memory, learning word list and prospective memory paradigms. In terms of verbal declarative memory, it has been found that BD is associated with poorer verbal declarative memory, regardless of sex (Parada, Corral, Caamaño-Isorna, Mota, Crego, Holguín, et al., 2011). These differences are

maintained after two years of follow-up in subjects who persisted in the BD pattern of consumption but not among the ones who left it (Mota et al., 2013). This finding is the first recovery index of cognitive function after the abandonment of the BD pattern in young people. With visual declarative memory tasks it has also found lower performance of young BDs in pared associate learning (Scaife & Duka, 2009) and drawn objects memory (Hartley et al., 2004). Regarding learning word list, three studies found a lower performance in young BD than in their peer controls (García-Moreno, Expósito, Sanhueza, & Angulo, 2008; García-Moreno, Expósito, Sanhueza, & Gil Hernandez, 2009; Sneider, Cohen-Gilbert, Crowley, Paul, & Silveri, 2013). And finally, a single study on prospective memory has reported greater difficulty of the BD group remembering location-action combinations compared to the control group (Heffernan et al., 2010).

The executive functions are the cognitive processes that have generated more interest regarding possible consequences of BD during youth. Different research groups have found worse performance of BD subjects in verbal working memory (García-Moreno et al., 2008, 2009; Parada et al., 2012; Sanhueza et al., 2011), visuospatial working memory (García-Moreno et al., 2008, 2009; Scaife & Duka, 2009), cognitive flexibility (Scaife & Duka, 2009), inhibitory control (García-Moreno et al., 2008, 2009; Sanhueza et al., 2011) and decision making (Goudriaan, Grekin, & Sher, 2007; Johnson et al., 2008; Xiao et al., 2009).

Taken together, BD during adolescence seems to affect mainly memory and executive functions depending on mesial-temporal and prefrontal areas. Therefore, these different neuropsychological studies suggest that the alcohol pattern consumption BD is generally linked at a lower performance in tasks involving attention, learning, executive skills and decision making.

1.3.2.Binge drinking and Neurofunctional studies

fMRI studies

Along with structural neuroimaging studies, over recent years, there has begun to be studied the consequences of BD through fMRI. A total of four studies have found differences in brain activation between BDs and controls although there was no difference in the performance of the task, during a coding of pairs of words task (Alecia D Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010a; Alecia Dager Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011) and a visual working memory task (Campanella et al., 2013; Squeglia, Schweinsburg, Pulido, & Tapert, 2011). The authors of these studies support the hypothesis that differences in brain activity allows the BD group to have an equivalent behavioral performance to the control group. Conversely, a different fMRI study found differences in brain activity as well as differences in the performance of a decision making task (Johnson et al., 2008).

Finally, two longitudinal studies open to debate whether the anomalies observed in brain function in adolescents BDs are result of the intensive alcohol consumption or a vulnerability factor prior to the start of the BD consumption. The first one considered that the differences in brain activity between groups are prior to the start of BD consumption and, therefore, constitute a risk factor for future addictive behaviors (Squeglia et al., 2012). On the other hand, in the second longitudinal study (Wetherill, Squeglia, Yang, & Tapert, 2013), the authors defended that the differences between groups are a consequence of BD consumption pattern.

Electrophysiological studies

In line with the fMRI results, psychophysiological studies using electroencephalography (EEG) have also confirmed the presence of abnormalities in brain function in young BDs as compared with controls.

A single study evaluated by EEG brain activity function during resting state and these authors found that intensive BDs (with a consumption of more than 10 SUD in a two hours interval, more than one occasion in the past six months) had more spectral power in delta (0-4 Hz) and fast beta (20-35 Hz) frequency bands compared with light drinkers and moderate BDs. These authors interpret the results as a potential biomarker of alcoholism risk (Courtney & Polich, 2010).

Using event-related potentials (ERP) it has been found that brain electrical activity associated with different cognitive functions is affected in young BDs. Several studies have found that different ERP components associated with perceptual processes (P1/N1), attentional processes (N2/P3),

working memory (P3) and inhibitory control (NoGo-P3) have abnormal amplitude and/or latency values in young BDs compared to their peer controls (Crego et al., 2009, 2010, 2012; Ehlers et al., 2007; E López-Caneda et al., 2013; Eduardo López-Caneda et al., 2012; P Maurage et al., 2012; Pierre Maurage, Pesenti, Philippot, Joassin, & Campanella, 2009; Petit et al., 2012; Petit, Maurage, Kornreich, Verbanck, & Campanella, 2013; Smith & Mattick, 2013; Watson, Sweeney, & Louis, 2014). However, given the many differences between the studies, as the different experimental paradigms or the different compositions and sample sizes, there is no unanimity on the results and their interpretations form these ERPs studies.

1.3.3. Binge drinking and Neurostructural studies

Currently, most of the neurostructural studies have been carried out in young people with alcohol abuse or dependence. For the moment, there are still very few studies on the population of BD adolescents and they are divided into diffusion tensor imaging (DTI), to evaluate the integrity of white matter, and MRI studies, to assess the density of the cortical gray matter.

The results obtained by DTI showed that adolescent with BD pattern have lower fractional anisotropy (a value reflecting fiber density, axonal diameter and myelination in white matter) in various fascicles including association, projection and commissural tracts (J Jacobus et al., 2009; McQueeny et al., 2009). Regarding MRI studies, the results indicate the presence of structural alterations associated with this type of consumption in the cerebellum (Lisdahl, Thayer, Squeglia, McQueeny, & Tapert, 2013), frontal cortex (Squeglia et al., 2012) and ventral striatum (Howell et al., 2013).

Given the paucity of neurostructural studies, new studies are needed and also it is important to clarify whether the observed alterations could compromise the cognitive functioning of this population.

1.4. Neuroimaging

1.4.1. Electrophysiological basis of brain activity

The brain is an enormously complex biological system and currently it is one of the major targets within the scientific community. Its complexity goes beyond its appearance to the naked eye. The human brain contains between 86-100 billions of neurons (Pelvig, Pakkenberg, Stark, & Pakkenberg, 2008), which are the units of function in the nervous system as it was first enunciated by Cajal in 1888 (Ramón y Cajal, 1888). From a macroscopic point of view, the brain contains three types of components: grey matter, white matter and cerebrospinal fluid (see figure 1-4).

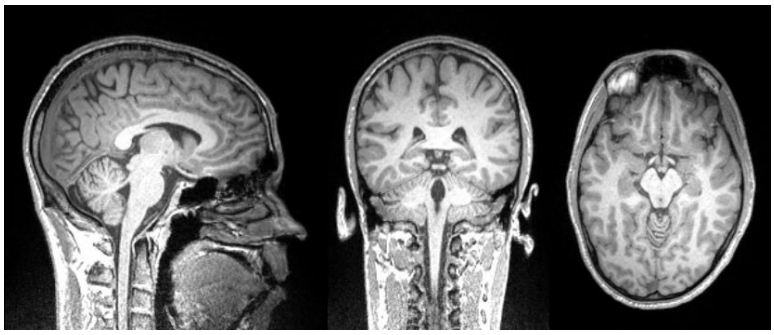

Figure 1-4 T1 MRI imaging.
Sagittal plane (left), coronal plane (center) and horizontal plane (right) of the human brain.

Grey matter consists of neuronal cell bodies, glial cells (*astroglia*, *oligodendrocytes*, *microglial cells* and *ependymal cells*) and capillaries. It is considered the responsible of the information processing as it contains most of the neuronal cell bodies, and it is mainly distributed at the surface of the cerebral hemispheres (cerebral cortex). The grey matter is distinguished from white matter in that it contains numerous cell bodies and very few myelinated axons, whereas white matter contains relatively very few cell bodies and is composed mainly of myelinated axon tracts, the highways of the information transfer in the brain. The characteristic white color arises principally from the myelin, which consists of multiple layers of closely opposed glial membranes, and acts as an electrical insulator speeding up the action potential conduction.

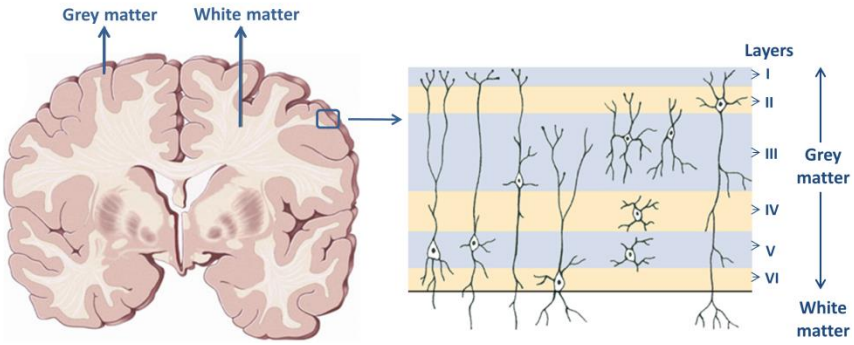

Figure 1-5 Cerebral cortex layers
Layer I: molecular; layer II: external granular; layer III: external pyramidal; layer IV: internal granular; layer VI: multiform

From a histologically point of view, the cerebral cortex is differentiated into six horizontal layers, (from I to VI) segregated principally by cell type and neuronal connections (see figure 1-5). The pyramidal neurons produce the electrophysiological signals that can be measured from the scalp with EEG/MEG. The neocortex contains two primary types of neurons, excitatory pyramidal neurons (~80%) and inhibitory interneurons (~20%). These neurons receive inputs from and connect to tens of thousands of other cells (Peters & Jones, 1984) and are arranged in the form of a palisade with their apical dendrites parallel to each other and perpendicular to the cortical surface (Lopes da Silva, 2013). This specific symmetry allows to thousands of pyramidal neurons synchronously activated add the longitudinal components of their postsynaptic potential currents (named principal currents) creating a laminar current along the main axes of the neurons (M. Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Murakami & Okada, 2006). This laminar current is strong enough (≈ 10nA) to generates an electromagnetic *open field* (Lorente de No, 1947) that can extend over long distances and be measured by the EEG/MEG systems. The influence of the action potentials in the generation of the EEG/MEG signals is negligible because they are too fast (1-2ms) to allow their synchronization over a neuronal assembly, and their quadruple nature imply a rapid decay with distance in comparison to the dipole nature of the postsynaptic activity ($1/r^4$ vs $1/r^3$).

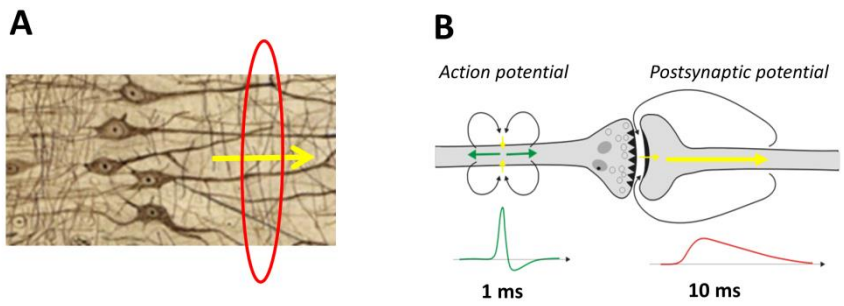

Figure 1-6 Electrical activation of pyramidal neurons.
A) Spatial distribution of apical dendrites. The summation of electric current (yellow arrow) generates a perpendicular magnetic field (red circle). B) Only the postsynaptic potentials last enough so it can produce a detectable magnetic field from the scalp.

Thus, the main generators of the magnetic field measured with MEG are the primary intracellular currents from the neurons oriented tangentially to the scalp and typically located in the sulci because the resulting magnetic field emerge perpendicular to the scalp surface (M. S. Hämäläinen & Ilmoniemi, 1994; Lopes da Silva, 2013). In the case of EEG, the main generators are the extracellular currents that can spread to the scalp surface (Lopes da Silva, 2013).

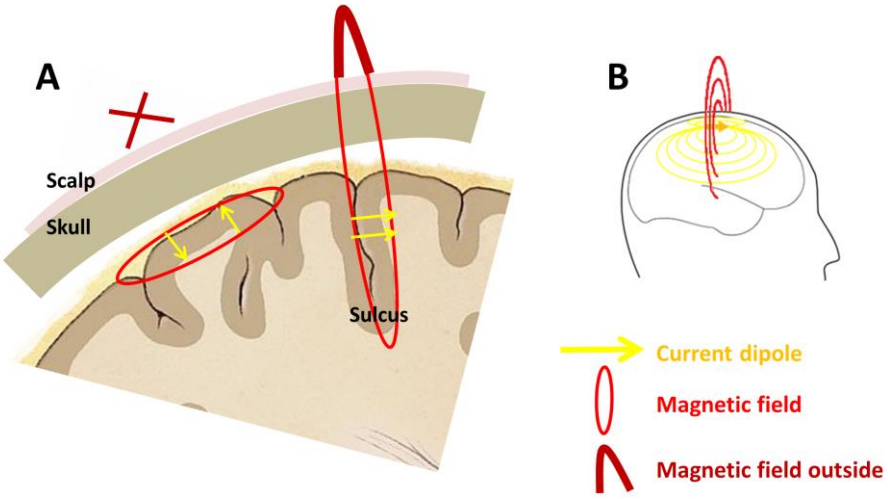

Figure 1-7 Orientation of the electric and magnetic field.
A, B) Given the spatial distribution of the apical dendrites, from the scalp it can only be detected the magnetic field produced by neurons which are in the sulcus.

1.4.2.Oscillatory brain activity

The brain has constant activity, either sleeping or during vigil, in the presence or absence of obvious stimulation. The first historical landmark in the development of the electrophysiology was

the tracing of fluctuating potentials in animals in 1875 by R. Caton (Niedermeyer, 1993). In 1929, Hans Berger made the first human EEG measurements, and described that the prominent oscillations in the brain oscillated at approximately 10 Hz and he named them *alpha* oscillations (Berger, 1929). Berger noted that when a subject closed his eyes, in a state of relaxation, the *alpha* rhythm increased. In the contrary, if the subject left the relaxation and opened his eyes, *alpha* was replaced by faster waves (beta rhythm). The oscillatory behavior of the electrophysiological brain activity relies on the preference of the neurons to form dynamical assemblies that tend to work in synchrony (Lopes da Silva, 2013). These interconnected neuronal assemblies are the basis of the functional brain network, and the synchronous oscillations are the most efficient way to produce or enhance temporal correlations between neurons (Buzsáki, Anastassiou, & Koch, 2012). The term oscillation refers to rhythmic alternations in the excitability of neuronal ensembles, and can be perceived on many temporal and spatial scales (F Varela, Lachaux, Rodriguez, & Martinerie, 2001). The most relevant mechanism that produces oscillations in the brain in terms of EEG/MEG signals is the interaction between inhibitory interneurons and excitatory pyramidal cells that create an alternating balance between states of excitation and inhibition (Buzsáki, 2006; Cohen, 2014). Thus, brain rhythm patterns detected with EEG/MEG reflect the degree of synchronization in the neuronal activity. The more the activity is synchronized, the greater the sum of the electric/magnetic activity of neurons, therefore, wider the signal reaching the surface of the scalp. When the activity of neighboring neurons appear to be highly correlated, the emerged oscillations are due to a *local-scale synchronization* (Llinás, 1988), whereas the term *large-scale synchronization* involves the synchronization of the activities of distant neuronal ensembles (Bressler et al., 2001). These spatial scales give rise, respectively, to two main analysis frameworks: the quantification of the brain activity in a certain region of the scalp/brain, which will be further referred as regional activation framework, and the analysis of the communication patterns between different regions of the scalp/brain, which will be further named inter-regional connectivity framework. The first one is assessed directly through the analysis of the *amplitude* of the electromagnetic fields, and by means of *spectral analysis* which quantify the energy of each brain rhythm. The second one is more recent and is studied by applying mathematical methods that evaluate the degree of synchronization, *the connectivity*, between the EEG/MEG signals.

I. Regional activation framework

The quantification of brain activation in a certain location (e.g. beneath each EEG/MEG sensor or in a brain source) has been traditionally achieved from two points of view: 1) directly over the raw electrophysiological signals, the so-called time domain analysis; and 2) with the transformed signals into the frequency domain.

In EEG, the voltage, usually microvolts (μV), is a relative measure which corresponds with electric potential changes between each electrode and the reference electrode. On the contrary, MEG measures directly the magnetic field, generally femtotesla (fT), which emerges perpendicular to the scalp surface. The values of the voltage/magnetic fields over time create the waves which constitute the electrophysiological oscillations.

The temporal resolution of the wave (i.e. the minimum time between measurements) depends on the sampling rate (usually established between 250 and 1000 Hz) employed in the recording of the electrophysiological signals. In the time domain, the time resolution will be the same as the inverse of the sampling rate because each point is a direct measure of the brain activity. However, in the frequency domain the time resolution is lower because the spectral power in each time step is obtained taking into account the temporally surrounding activity (Cohen, 2014).

Regarding the spatial resolution, it will be difficult to fix the origin of the neuronal activity reflexed in the wave because there are several factors that might affect the accuracy of the measurements. Besides the number of sensors, the most important factor is that the voltage/magnetic field measured for a specific sensor do not correspond only with the activity immediately beneath it but with the sum of a mixture of activities originated in different brain regions, causing some spatial autocorrelation (strong correlation among activities at neighboring sensors).

The characterization of the electrophysiological signals relies on the consideration that there are multidimensional oscillations. Apart from time and space, brain oscillations are characterized by three parameters: 1) frequency, which refers to the number of cycles per unit of time; 2) power, which corresponds with the energy in a frequency band and is the squared amplitude of the oscillation; and 3) phase, the relative position of the wave at a time instant.

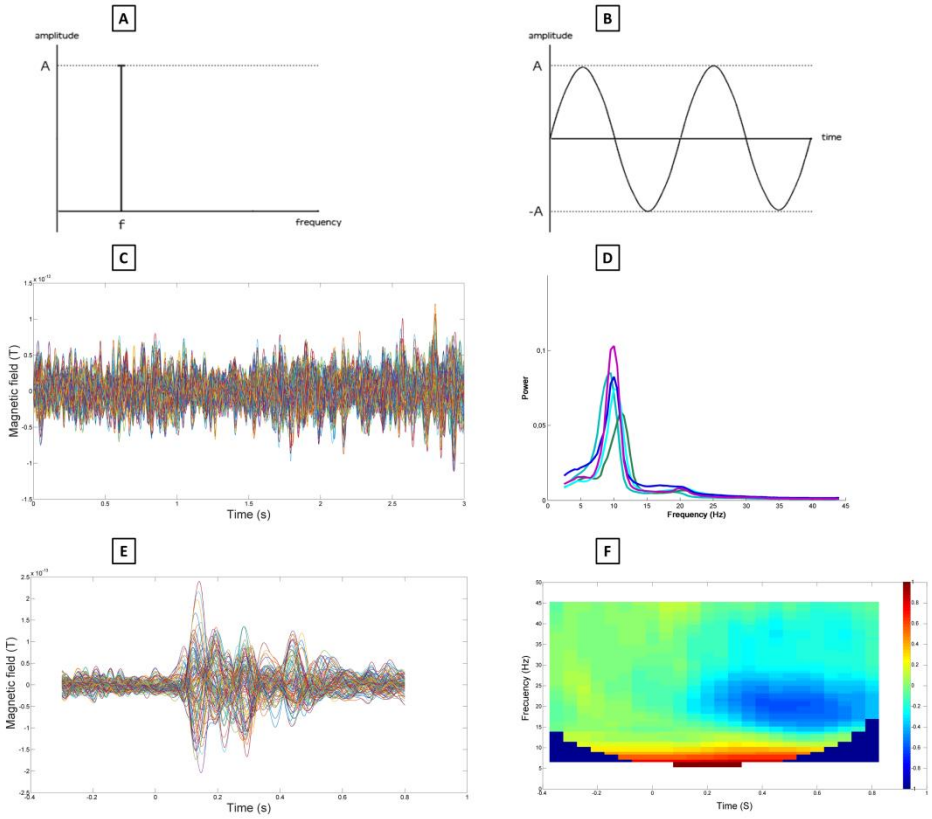

Figure 1-8 MEG signal representation.
A) Time domain. B) Frequency domain. C) Overlapping of MEG resting state signals of 3 seconds. D) Spectrogram of the MRG signal showed in C. E) Overlapping of MEG event-related brain activity. F) Time frequency plot of the signals depicted in E.

The transformation between the time-domain and the frequency-domain relies on the assumption that all oscillation can be decomposed, usually by means of the Fast Fourier Transform (FFT), into a sum of sub-oscillations (sinusoidal waves in FFT) with different amplitudes and frequencies. Accordingly, it is possible to estimate the contribution of different frequencies to the recorded electromagnetic activity. In the figure 1-8.A a wave in the time-domain is represented in each time step for an amplitude value which corresponds with the voltage/magnetic field. When the signal is transformed to the frequency-domain (figure 1-8.B), the amplitude now corresponds with the power at each frequency. In this case, as the wave is monochromatic (i.e. has a unique frequency), the spectrogram has only one value stating that the whole energy is emitted at the same frequency. In addition, as the properties of the wave depicted in 1-8.A do not change over time, the time is neglected because the whole time window was employed to estimate the spectral power. This spectrogram is used in specific situations as in brain resting state activity which can be considered stationary (this activity is further explained in the text).

In the 1-8.C section, an overlapping of 102 resting state MEG signals is depicted, and the corresponding spectrogram for 5 of these signals is showed in 1-8.D where the alpha peak appears clearly around 10 Hz. When the signals are not stationary it is necessary to fix a starting point to create a time-locking. The figure 1-8.E section is displaying the overlapping of several MEG signals evoked by a stimulus during the performance of a cognitive task. In this case, each MEG signal is an average across repetitions of the same experiment called an Event Related Field (ERF) where the event is defined by the configuration of the task and fixes a specific origin of time, which phase-locking the activity. In this case, the spectral estimation is performed by applying time-frequency analysis methods as the Short-Time Fourier Transform (STFT), or wavelets analysis. In the 1-8.F section, a time-frequency-response (TFR) plot shows 3-dimmensions: power (color), frequency and time.

In general, the electrophysiological signals are broadband filtered in order to remove the high-frequency artifacts and low-frequency drifts, and usually notch filtered at the frequency of the electric line (50Hz or 60Hz). In time domain the averaging across trials constitutes a low-pass filter because the non-phase-locked activity is dismissed in the averaging, and the activity with frequencies above 15 Hz tends to be non-phase locked (Cohen, 2014).

Although the brain works at multiple time scales, the most commonly studied brain frequency bands in humans include *delta* [0.05-4 Hz], *theta* [4-7 Hz], *alpha* [8-12 Hz] *beta* [13-30 Hz] and *gamma* [>30 Hz] where the borders have been established according to neurobiological mechanism of brain oscillations and clinical studies (Buzsáki, 2006; Lopes da Silva, 2013). (See figure 1-9).

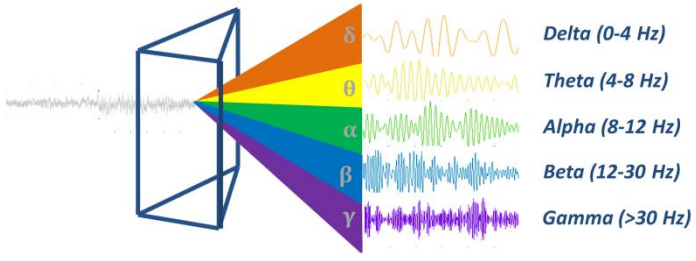

Figure 1-9 Classical frequency bands studied with EEG and MEG.

Oscillatory activity at different frequency bands seems to be involved in different functional significance and cognitive functions (Baars & Gage, 2013; Cacioppo, Tassinary, & Berntson, 2007; Cohen, 2014; W Klimesch, 1999; Niedermeyer, 1993; Schürmann & Başar, 2001). It has been argued that it is not possible to assign a single function to a given type of oscillatory activity since

brain functions arise form series of superimposed oscillations in different frequency ranges. Moreover, several studies have reported that individual variability in peak frequencies correlated with different parameters of cognitive performance and brain structural integrity (Cohen, 2014). Below, the different functional characteristics of the classical frequency bands are described.

Delta band (0-4 Hz)

In the healthy adult brain, slow waves are typical of deep, unconscious sleep and also appear in epileptic seizures and loss of consciousness. In addition, the predominance of delta rhythms has been associated with neurological pathology, as brain lesions or tumors (Fernández-Bouzas et al., 1999). While sleep disorders are the most popular topics for the study of delta in adult humans, much interest has also been drawn to gestation and early child development. Delta is the dominant activity in infants during the first two years of life. In fact, delta oscillations are dominant during the third trimester of gestation (Scher, 2008) and decrease progressively during childhood (John et al., 1980). Abnormally high delta power in children can be indicative of various developmental disorders such as attention-deficit/hyperactivity disorder (Barry, Clarke, & Johnstone, 2003). These rhythms are mainly located in the frontal areas in adults and in the posterior areas of the brain in child, and can be principally considered an inhibitory rhythm.

Theta band (4-7 Hz)

Theta rhythm is particularly prominent in the hippocampus and adjacent limbic structures involved in encoding and retrieval of episodic, spatial and working memory (Hasselmo & Eichenbaum, 2005; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999) as well as executive functions during inhibitory control (Brier et al., 2010; Kirmizi-Alsan et al., 2006) and in response to higher working memory load (Jensen & Tesche, 2002; McEvoy, Pellouchoud, Smith, & Gevins, 2001). In terms of its location in the brain, there are two main theta rhythms (Schacter, 1977). One widespread distributed across the scalp and related with low-attentional states and impaired information processing. The other one, located in the frontal midline of the scalp, has been linked with focused attention and effective stimulus processing.

Alpha band (8-12 Hz)

Alpha oscillations are the dominant rhythm during states of relaxed wakefulness and have their greatest amplitude in the posterior-occipital region when a subject closes his eyes. This led scientists to believe that alpha oscillations were just a representation of the idling brain. However, this vision has faded, as the role of alpha oscillations in perception and cognition has become more important (Bonnefond & Jensen, 2013; Lopes da Silva, 2013). The main feature of alpha rhythm is

that is strongly modulated by eye opening, which triggers a decrease in its power. Moreover, attention to visual stimuli causes changes in alpha activity, therefore, when a subject attends to the left hemifield, alpha power decreases in the right occipito-parietal cortex (responsible for the left hemifield) while it increases in the left occipito-parietal cortex (responsible for the right hemifield) (Rihs, Michel, & Thut, 2009; Worden, Foxe, Wang, & Simpson, 2000). The fact that alpha power decrease over task-relevant regions and increase over task-irrelevant regions seems to have a functional role, as it relates to task accuracy performance (Ergenoglu et al., 2004). This lead to the hypothesis that alpha power has an inhibiting role in cognition (Lopes da Silva, 2013).

Beta band (12-30 Hz)

Beta band presents mainly a frontal-central distribution and has been traditionally linked to motor control (Engel & Fries, 2010). Prior and during a voluntary movement (and also during imagined movements) beta amplitude decreases in the motor cortex (de Lange, Jensen, Bauer, & Toni, 2008). Upon movement termination, beta power rapidly exceeds pre-movements levels before returning to the resting-state (Pfurtscheller, Pregenzer, & Neuper, 1994) in adult participants. This process has been termed event-related synchronization and when observed in the context of movement task, has been called post-movement beta rebound (PMBR). This transient PMBR can be observed from bi-lateral sensorimotor cortex, but is stronger in contralateral sensorimotor regions, typically rising ~300 ms after movement termination. Although the origin and functional significance of PMBR is not clear, likely represents a state of motor cortical inhibition and is assumed to index the location of cortical activity participating in movement preparation and performance. Importantly, PMBR has been shown to be represent a marker of functional brain development, increasing in power as a function of age in healthy individuals (Gaetz, Macdonald, Cheyne, & Snead, 2010) and therefore, PMBR may offer a fundamental developmental measure of the inhibitory system in the brain, making it an appealing investigation target in individuals with developmental disorders.

Gamma (>30 Hz)

Although gamma rhythm is known since the beginning of the last century, it has not been studied as its role in cognitive processing since few years ago. The responsible for the scientific interest that this frequency band has generated is the *binding hypothesis.* This theory explains the brain´s ability to integrate different sensory characteristics (e.g. Color or shape) into a coherent percept. This is possible because gamma band has a very short period of oscillation and offers a temporal precision of milliseconds to integrate the synchronized activation of neural assemblies that

encode separate features of the stimulus (Buzsáki & Wang, 2012; Fries, Nikolić, & Singer, 2007). Gamma band is considered an indicator of brain activation as it is correlated with glucose metabolism (Oakes et al., 2004), and several mental processes as perception (Rodriguez et al., 1999) or learning (Miltner, Braun, Arnold, Witte, & Taub, 1999).

II. Inter-regional connectivity framework

Traditionally it has been thought that the human brain is organized into functionally specialized regions, supported by the idea that localized brain injury induces damage on selectively cognitive processes. In the last decade, this paradigm is evolving into a new perspective that describes the brain as a complex biological system that uses dynamic networks as the basis of the cognitive functions (Karl J. Friston, 1994; Francisco Varela, Lachaux, Rodriguez, & Martinerie, 2001; Yuste, 2015). Therefore, cognitive processing requires a transient integration of numerous functional areas widely distributed over the brain and in constant interaction with each other where a balance of *integration* and *specialization* has to be maintained. Thus, brain activity reflects the activation of several networks that are communicated to each other. Long range communication or *synchronization* between different networks has been stated as the mechanism for communication and integration of the information in the brain (Francisco Varela et al., 2001).

In order to describe how brain regions are coordinated to support higher cognitive functions, the term connectivity has been coined (K J Friston, 2001; Karl J. Friston, 1994). Functional Connectivity (FC) reflects the statistical interdependencies between certain pair of electrophysiological signals, giving information about functional interactions between different brain regions. This methodology does not give information about the direction of the interaction or whether a region is driving the interaction over the other; therefore FC is a symmetrical measure. Alternatively, the directionality of the coupling can be assessed through the Effective Connectivity (EC), which implies that the EC measures causality between the measured oscillatory signals. As others measurements, FC and EC can be studied during the performance of active tasks as well as during resting state, condition in which the participant is not performing any active task and is simply instructed to remain still, with eyes closed or open while fixating a cross. Additionally to FC and EC, Structural Connectivity (SC) gives information about physical connections linking different neuronal assemblies, which informs about the anatomical structure of brain networks.

How these three connectivity concepts coexist and interrelate is an elusive goal so we must be cautious when relating the different types of connectivity. It is well known that neither FC nor EC

between two different regions do not entail the existence of any physical connection between that areas, instead each measurement does give information about the existence of a relationship (causal in the case of EC) between different recorded signals. In the present dissertation, the term connectivity will always be referring to FC as it is the predominant methodology employed in the experiments of this dissertation. In the second experiment (section 3), where SC was employed alongside FC, the term connectivity will be specified by SC or FC in each case.

FC relies on the measurement of the statistical interdependencies between a certain pair of time series simultaneously recorded. Depending on the nature of those interdependencies, the synchronization between the signals can be of different classes: phase synchronization (PS) or amplitude correlation (AC). PS is widely used in neuroscience (Francisco Varela et al., 2001), and refers to a situation when there is an interdependence between the phases of the signals, even though their amplitudes may remain uncorrelated (Pereda, Quiroga, & Bhattacharya, 2005). In the experiments carried out in this dissertation the method employed to assess the FC has been the Phase Locking Value (PLV) or mean phase coherence (Lachaux, Rodriguez, Martinerie, & Varela, 1999; Mormann, Lehnertz, David, & E. Elger, 2000). The PLV offers a straightforward estimation of the averaged phase coupling of each frequency band among different electrophysiological brain signals. It is a method largely employed in EEG/MEG literature and offers a considerable test-retest reliability (Garcés, Martín-Buro, & Maestú, 2016). The algorithm details are shown in the methods section of the corresponding experiments.

On the other hand, amplitude correlation is a measure of the co-modulation of the amplitude envelopes (the power) of oscillations in two areas (Bruns, Eckhorn, Jokeit, & Ebner, 2000). Although the interpretation of AC is less clear than the mechanistic interpretation of PC, AC is an informative index of the large-scale cortical interactions that mediate cognition. Technically, PC and AC are independent of one another. For instance, the amplitude envelope of the oscillatory responses of two regions can co-vary strongly even if their phases are randomly distributed; and the reverse also can be true.

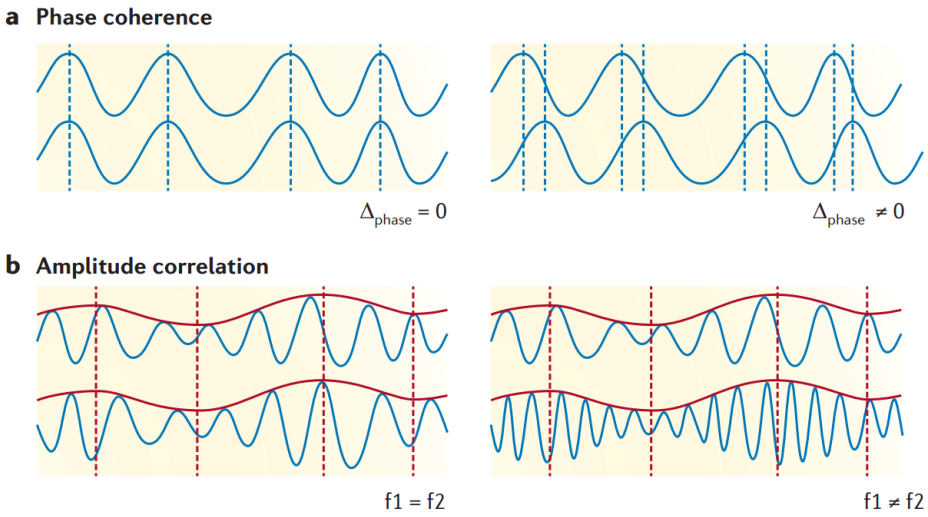

Figure 1-10 Phase coherence and amplitude correlations of oscillations. (Siegel, Donner, & Engel, 2012).
A. Phase correlation. Left: two oscillatory signals that are phase coherent with zero phase lag ($\Delta_{phase}=0$). Right: Phase coherent signals with non-zero phase lag ($\Delta_{phase}\neq 0$).
B. Amplitude correlation. The envelope correlations are shown in red of two simultaneous oscillatory signals. Left: Amplitude correlation is measured between oscillatory signals of the same underlying frequencies (f1=f2). Right: Amplitude correlations measured between signals of different frequencies (f1≠f2).

Default Mode Network

Brain networks combine strong local connectivity with efficient long-distance connections. These characteristics imply, based in the complex systems theory, that brain networks are cost-efficient small-world networks (Bullmore & Sporns, 2012; Cornelis J. Stam, 2014). Key concept are the highly connected nodes or regions, so-called *hubs* (Sporns, 2013), because they appeared to be of extremely importance in maintaining the functional integrity of the network (Cornelis J. Stam, 2014).

To date, the most studied brain network is the default mode network (DMN), for a review see (Rosazza & Minati, 2011). The DMN is highly active during resting state, when the brain is not involved in an externally imposed goal-directed activity, and it deactivates during task performance. In fact, it Is well known that under resting conditions, the brain is engaged in spontaneous activity which is not attributable to specific inputs or to the generation of specific output, but is intrinsically originated. An important question is what these spontaneous fluctuations represent. A reasonable hypothesis is that these fluctuations reflect spontaneous cognitive processes. In the absence of a task or a stimulus attracting our attention, we naturally tend to think on the recent past, to imagine future events or simply to wander with our thoughts.

In fact, the DMN has been associated to unconstrained cognitive processes, given that it is generally observed more active during passive cognitive states than during active task.

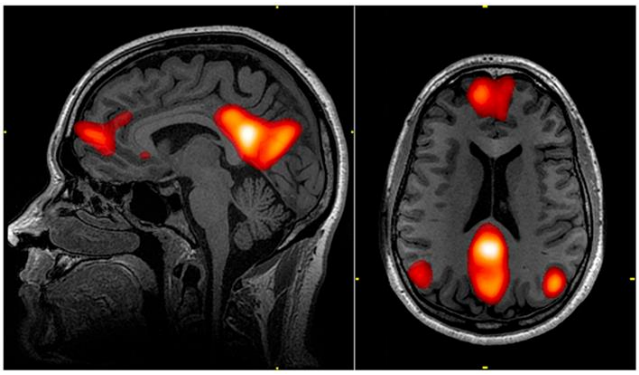

Figure 1-11 Areas involved in the Default Mode Network

The main brain regions activated in the DMN are the precuneus, the posterior and anterior cingulate cortex, the middle prefrontal cortex and the inferior parietal cortex (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Marcus E Raichle & Snyder, 2007). Since this network was first described in 2001 by Raichle (M E Raichle et al., 2001) the DMN has garnered increasing attention during last decade among the neuroscience community due to it has been found affected in several neurological conditions such as depression (Eyre et al., 2015), insomnia (Suh, Kim, Dang-Vu, Joo, & Shin, 2015), schizophrenia (Wang et al., 2015) or dementia (Garcés et al., 2014). Regarding alcohol consumption, the DMN has also been found clearly altered in chronic alcoholics (Müller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2015; Zhu, Cortes, Mathur, Tomasi, & Momenan, 2015; Zhu, Dutta, et al., 2015). Besides, acute alcohol intake also seems to affects the DMN (Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2016; Weber, Soreni, & Noseworthy, 2013; Zheng, Kong, Chen, Zhang, & Zheng, 2015) but up to now there is no evidence of DMN disruption in young binge drinkers.

1.4.3.Neuroimaging techniques

I. Magnetoencephalography

The Magnetoencephalography (MEG) is an entirely silent and noninvasive technique which detects weak magnetic fields from above the surface of the head produced by the synchronized neuronal activity. It is a direct measure of the brain activity with a time resolution of milliseconds and a spatial resolution approaching a few millimeters (Baars & Gage, 2013; Pievani, de Haan, Wu, Seeley, & Frisoni, 2011).

The magnitude of the magnetic fields generated by the brain activity fluctuates between 1fT and 100 pT (M. Hämäläinen et al., 1993). These magnetic fields are orders of magnitude (between 10^4-10^{10}) weaker than ambient magnetic fields, including the Earth´s magnetic field whose magnitude is approximately 25-65 μT. Thus, the measurement of the brain magnetic fields requires a sophisticated and highly sensitive system located inside a magnetically shielded room which is composed of different layers of aluminum and a nickel–iron soft magnetic alloy with very high permeability alloy called μ-metal (see Figure 1-12).

Figure 1-12 Elekta Magnetoencephalography system
Left: MEG shielded room, right: MEG system

The MEG system (see figure 1-13) is composed by three main components: the magnetic field sensors based on Superconducting Quantum Interference Devices (SQUID), the flux transducers, and the Dewar flask.

The SQUIDS are extremely sensitive sensors based on superconducting coils containing Josephson junctions (M. Hämäläinen et al., 1993; Zimmerman, Thiene, & Harding, 1970). Superconductivity is the property of certain materials that under specific circumstances (extremely low temperatures) reach a null electric resistance and become perfect diamagnetics. Accordingly, when a superconductor is placed in an external magnetic field generates a magnetic field that cancels, within the material, the external magnetic field. Thus, SQUIDs are able to convert, with high sensitivity, magnetic flux into voltage. However, SQUIDs do not measure directly the brain magnetic fields; this task relies on the flux transducers (see figure 1-13-B).

Flux transducers are composed by two superconductor coils with different size: 1) the bigger one called pick-up coil collects the magnetic flux with an enhanced signal to noise ratio due to its larger area; 2) the smaller one has the same size than the SQUID and projects the magnetic flux into the

SQUID. Besides from the amplification obtained with the larger area, the pick-up coils allow the availability of different spatial configurations without modifying the SQUID design that give rise to different measures of the neural magnetic fields. The simple case is the magnetometer, a single loop coil which is sensitive to the perpendicular magnetic fields. Gradiometer instead consists of two-loops coil aligned in a plane and with opposite winding sense of that the field detected is the subtraction of the field measured by each of the coil (see figure 1-13-C).

Finally, the Dewar flask is required to maintain the SQUIDS and flux transformers in a superconductor state. The Dewar flask is filled with liquid helium at its boiling temperature (4.2K) and it is thermally insulated in order to keep the MEG helmet at room temperature (see figure 1-13-A).

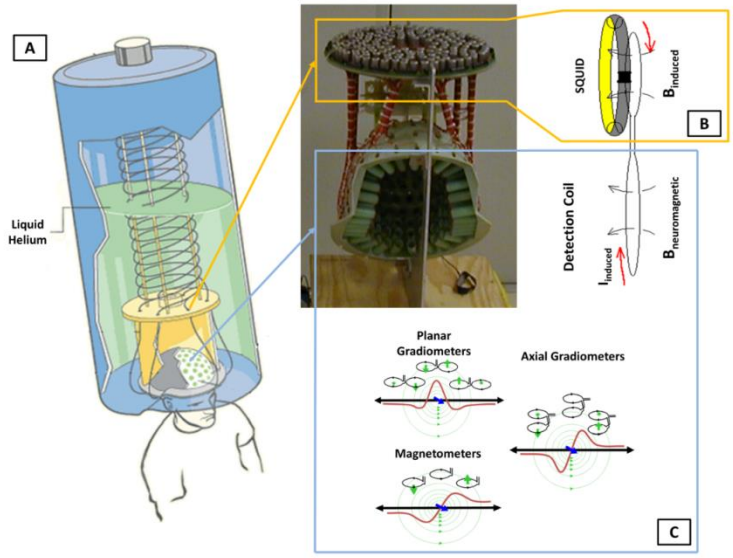

Figure 1-13 Main MEG system components
A) Dewar flask, B) SQUIDs, C) Flux transducers

In the MEG studies described in present dissertation a 360-channel Vectorview system (ElektaNeuromag) located at the Centre of Biomedical Technology (Madrid, Spain) was used. This MEG system comprised 102 detector units spread in a whole head MEG helmet. Each detector unit contains one magnetometer and two planar gradiometers in orthogonal directions. The system is shielded from external fields with a Vacummschmelze (Hanau, Germany) magnetic shielded room.

Experimental frameworks: sensor and source spaces

The MEG system measures the brain magnetic fields outside the scalp by means of several sensors (306 in the case of the Elekta Neuromag system) and therefore, the sensors space is the primary framework for the MEG signals analysis. The sensors space framework has some advantages as the direct measurements of the neural magnetic fields, the quite straightforward analysis or the not requirement of a structural MRI image. However, nowadays most of the research with MEG is carried out by calculating the brain locations that generated the magnetic fields recorded from the scalp, so-called sources space. Solving the distribution and dynamics of the cortical sources is more difficult and involves greater uncertainty than the sensor space because without constraints, has an unlimited number of solutions. Calculating the sources requires the solution of two problems. The first one is the forward problem which consists of the calculation of the scalp magnetic field generated by neuronal sources. Usually, it involves the use of a structural MRI image in order to obtain a realistic model of the head. The second problem is the solution of the *inverse problem* that solves the particular distribution and dynamics of the cortical sources. It is an ill posed problem because there are multiple solutions that are equally likely (i.e., a large number of combinations of intracerebral sources could result in the same topographical distribution of activity in the scalp). The problem is addressed by taking into account some assumptions about the distribution of the current sources modeled with specific constraints (Baillet, Mosher, & Leahy, 2001; Sekihara & Nagarajan, 2008).

II. Magnetic Resonance Imaging

The brain structural imaging is mainly studied by means of magnetic resonance imaging (MRI) which is capable of provide anatomical scans with a high resolution of about 1 mm^3. The physical principle is that a certain atomic nuclei can absorb and emit radio frequency energy when it is placed in an external magnetic field. The most common MR images use hydrogen atoms because they are abundant in water and fat, therefore, the typical MR image is a map with the location of water and fat in the brain. These images are used to create the head model of each subject which will support the anatomical constraints used in the solution of the forward problem. A different structural imaging made with MR system is the diffusion tensor imaging (DTI) which study of white matter tracts, mapping the physical connectivity network that underlies the brain activity. This process consists of the measurement of the spontaneous diffusion of water with special MR images. The physical principle relies in the tendency of water to diffuse more easily along white

matter tracts. Thus, by analyzing the water diffusion images it is possible to generate 3D maps of the white matter fibers in the brain.

Finally, besides from the pure structural imaging, the MR is capable to offer functional information through the measurement of changes associated with the blood flow by means of the functional magnetic resonance imaging (fMRI). The most common fMRI is based on the blood-oxygen-level dependent (BOLD) contrast, which offers information about the brain activity as a function of the oxygen level of the local blood circulation (hemodynamic response) related to energy use by the neurons.

III. Brain imaging techniques comparison

In the figure 1-14 a comparison among the different neuroimaging techniques is depicted in terms of spatial resolution, time resolution and degree of invasiveness. EEG and MEG are the only techniques capable to measure directly the brain activity. In particular, MEG has a minimum invasiveness, high time resolution with a good spatial resolution (about 5 mm). In addition, as the tissues surrounding the brain have constant magnetic permeability, the solution of the inverse problem in MEG is easier than in EEG where an accurate head model is required due to the different electrical conductivities of the cerebrospinal fluid, skull, and skin that affect the electric fields. The MRI has high spatial resolution, very low time resolution and in the case of the functional imaging, the fMRI is an indirect measurement of the brain activity. Finally Positron Emission Tomography (PET) is a functional imaging technique employed to study metabolic processes in the brain (e.g. glucose metabolism), anomalous protein aggregations (as amyloid plaques) or any other concentration of biologically active molecules. The invasiveness is significant given that is a nuclear medicine technique that requires the injection of a radionuclide (tracer) that joins to the molecule of interest.

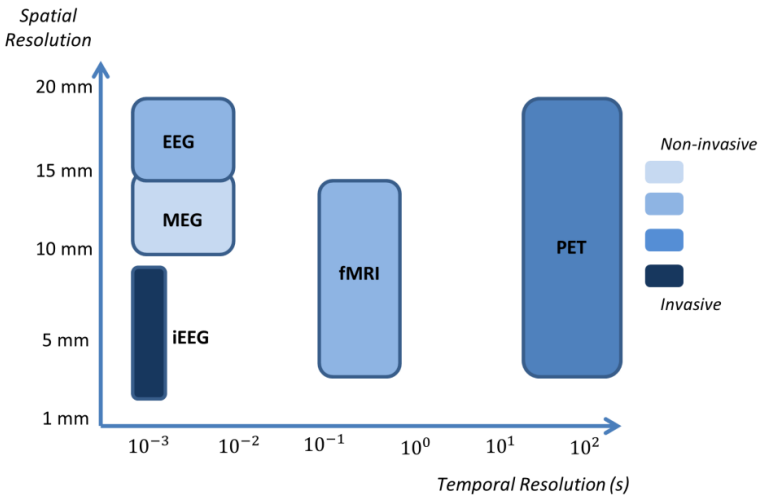

Figure 1-14 Invasiveness, spatial and temporal resolutions
EEG: Electroencephalography, iEEG: intracranial electroencephalography, MEG: Magnetoencephalography, fMRI: functional Magnetic Resonance Image, PET: Positron emission tomography). Color indicates the invasiveness; light blue: non-invasive, dark blue: invasive)

2. EXPERIMENTAL STUDY I

Exploratory Analysis of Power Spectrum and Functional Connectivity during Resting State in Yong Binge Drinkers

2.1. Aims and hypothesis

The main goal of this first study was to characterize the possible brain damage associated with alcohol binge drinking by means of exploring the brain magnetic patterns of young binge drinkers and control aged matched subjects. To this end, we analyzed functional connectivity and relative power spectra profiles measured with Magnetoencephalography during eyes-closed resting state. To the best of our knowledge, this is the is the first neurophysiological investigation that assesses the power spectra and the functional connectivity pattern during brain resting state in binge drinkers compared to light or nondrinker controls. We tested the hypothesis that the binge drinking pattern of alcohol consumption may induce anomalies in the oscillatory and synchronized brain activity, even in early ages.

2.2. Methods

2.2.1. Participants

MEG signals were obtained from 73 first-year students of the University Complutense of Madrid: 35 BDs (18 females) and 38 control subjects (17 females). They were divided into BD group and a control group according to a questionnaire and a semi-structured interview inquiring about alcohol and other drug consumption habits. Participants were asked to cover a record of daily consumption indicating what they drank, the quantity and for how long (hours). Their blood alcohol consumption was calculated based on the information of dinking episodes of the last six months and according to the following algorithm:

$$BAC = \left(\frac{G\ of\ alcohol\ consumed}{Weight\ in\ Kg\ \times\ r}\right) - mr\ \times hours \qquad [2.1]$$

Were *r* is a constant with value 0.68 for male 0.55 for female and *mr* is the metabolization ratio with value 0.15 for male and 0.18 for female. We considered the BAC value as a rough index representing the BD level of each subject. Participants reaching BAC of 0.08% or above, which correspond to a BD episode, at least once during the last month were classified as BD. On the other hand, the control group consisted of students who never achieved that alcohol concentration. The average time that the BD group had been drinking was 14.98 ± 1.17, making it a very homogeneous history of consumption, so this question would not be a contaminating variable. Demographic data are shown in Table 1.

Table 2-1 Demographic, tobacco and alcohol consumption data.

	Controls	***Binge Drinkers***
N (females)	28 (17)	35 (18)
Age	18	18
Tobacco smokers	0	4
BAC in a drinking episode	0.0147 ± 0.024	0.1537 ± 0.0413

All volunteers provided written informed consent prior to assessment. Participants were asked to refrain from alcohol consumption for, at least, 24 h prior to MEG recordings. Subjects were submitted to breathalyzer test and the assessment was only performed after verifying a 0.00% breath alcohol level.

The exclusionary criteria of the study are shown in Table 2. In order to minimize the possible influence of genetic predisposition for alcoholism, participants were questioned about their personal and family history of alcoholism (FHA). Personal history of psychopathological disorders (axes 1 and 2) were excluded according to DSM-IV-TR criteria and psychopathological traits were assessed by the Symptom Checklist-90 Revised questionnaire (SCL-90-R). In addition, it was verified that subjects neither had any disease affecting cognitive functioning or neurological disorders nor were taking any medicine with psychoactive effects. Besides, they answered the Alcohol Use Disorders Identification Test (AUDIT) and subjects who scored 20 or above were excluded for having AUD. Tobacco consumption was not an exclusion criterion but a controlled variable. According to the Syndrome Nicotine Dependence Scale (NDSS-S), four participants fulfilled the criterion of nicotine dependence, all belonging to the BD group. Regarding cannabis consumption, although only regular cannabis users were excluded of the sample, no subject consumed even occasionally.

Table 2-2 Exclusion criteria applied in this study.

Medical conditions affecting the normal cognitive functioning
Personal history of neurological disorder
Personal history of psychopathological disorders (according to DSM-IV)
Family history of major psychopathological disorders in first degree relatives
Family history of first or second degree of alcoholism or substance abuse
Use of illegal drugs (except occasional cannabis consumption)
Regular consumption of medical drugs with psychoactive effect
Motor or sensory disabilities uncorrected
AUDIT scores ≥ 20

2.2.2.MEG recordings

Four minutes of resting state with closed-eyes were acquired at 100 Hz sampling rate (online band pass filtering at 0.1-330 Hz) with a 306-channel Vectorview system (ElektaNeuromag) which combines two orthogonal, planar gradiometers and one magnetometer.

Only magnetometers (102 channels) information was analyzed in this study. The system was housed in a magnetically shielded room (VacuumSchmelzGmhH, Hanua, Germany). The movement was controlled by means of four head-position indicator (HPI) coils and subject´s headshape placed on three anatomical locations (nasion and both preauricular points) was

defined using a 3D digitizer (FastrakPolhemus). Ocular movements were tracked by means of two bipolar electrodes. Recordings were submitted to Maxfilter software (v 2.2, correlation threshold = 0.9, time window = 10 s) in order to remove external noise with the temporal extension of the signal space separation method with movement compensation (Taulu & Simola, 2006). Resting state magnetometer´s data was automatically scanned for ocular, muscle and jump artifacts with Fieldtrip package (Oostenveld, Fries, Maris, & Schoffelen, 2011). Artifact-free data were segmented into continuous 4-s fragments (trials). The MEG power spectrum (1-45 Hz) was computed for all trials (see below for details). An experienced technician, blinded to the subjects´ group, carried out a visual inspection over the raw data and the spectrum. Those trials with noisy raw signal or aberrant power profile were dismissed. Finally, only MEG recordings with at least 15 clean trials (1 min of brain activity) were kept for further analyses. The number of surviving trials did not differ significantly between groups (control group: 39.1 ± 7.4; binge drinking group: 37.6 ± 8.9; p= 0.75). Matlab version 8.0 (Math-works, Natick, MA, USA) was used for the analysis with custom-written scripts.

2.2.3.Power spectrum

MEG power spectrum was computed through Fieldtrip with a variable frequency of interest range of 0.5 Hz steps from 2 to 25 Hz and 1 Hz steps from 26 to 45 Hz. The average frequency content of each trial was obtained through a multitaper method (mtmfft) with discrete prolate spheroidal sequences (dpss) as windowing function and 1 Hz smoothing. These power spectra were averaged across trials, obtaining for each subject a matrix whose dimensions were 102 channels x 67 frequency steps. Finally, the power spectrum was normalized with the sum of the spectral power in the 2-45 Hz range.

2.2.4.Phase locking value (PLV)

In this study, the functional connectivity was measured by PLV in the following frequency bands: delta (2-3.9 Hz), theta (4.1-7.9 Hz), alpha (8.1-11.9 Hz) and beta (12.1- 29.9 Hz). First, the time series were filtered with a Finite Impulse Response filter of order 300 designed with a Hamming window. The filter was applied using a two-pass procedure over the whole 4-min registers, in order to avoid phase distortion and edge effects. The starting data set consisted in matrices with dimensions: 102 channels x 4000 samples x 4 frequency bands x trials. Then, for each frequency band and trial, we have calculated PLV via the following procedure: 1) for each sensor j = 1,…,102, the phase of the signal x_j (t) was extracted by means of Hilbert transform:

$$Z_j(t) = x_j(t) + i \cdot Hilbert\left(x_j(t)\right) = A_j(t) \cdot e^{i\varphi j(t)} \quad [2.2]$$

2) the synchronization between a pair of phases $\varphi_j(t)$ and $\varphi_k(t)$ was calculated with the following expression:

$$\mathrm{PLV} = \frac{1}{M}\left|\sum_{m=1}^{M} e^{i(\varphi_j(t_m)-\varphi_k(t_m))}\right| \quad [2.3]$$

Were M= 4000 is the number of samples in the time series (4s sampled at 1000 Hz). Finally, the results were averaged across trials ending up with symmetrical 102 channels x 102 channels connectivity matrices for subject and frequency band.

2.2.5.Statistical analysis

In both cases (PS and FC analysis), the first step consisted in transforming, prior to the statistical test, the values (power or PLV) by means of

$$x = \log\left(\frac{x}{1-x}\right) \quad [2.4]$$

in order to obtain values following a normal distribution.

IV. PS analysis

In order to accomplish a data-driven analysis of the power differences between groups, we used a methodology designed for EEG/MEG data extracted from the cluster based nonparametric permutation test described by Maris and Oostenveld (Maris & Oostenveld, 2007). A similar methodology has been employed successfully in previous studies (Coullaut-Valera et al., 2014; Cuesta, Barabash, et al., 2014; López et al., 2014).

First, an exploratory pairwise *t*-test was calculated per each channel in each frequency step. Those comparisons which were found to show significant differences between groups ($p < 0.05$) were clustered according to a criterion of spatial (each cluster should contain at least three contiguous and significant sensors) and frequency adjacency (the difference between pairs of groups must remain significant during at least a 2 z-interval which corresponds to 4 frequency steps). Then, the obtained power values were submitted to a nonparametric permutation test. This test consisted in assigning randomly 2000 times the power values to the original groups. The sum of *t*-values over each cluster in the original data set was compared with the same measure in the randomized data. Therefore, for each cluster, the proportion of randomizations with *t*-values higher than the ones in the original data corresponds to the final *p*-value. Finally, with the aim of characterizing the significant differences between groups in each cluster and frequency range; we carried out

another *t*-test between the averaged power values in the significant clusters and within the significant frequency ranges. This comparison was submitted as well to the non-parametric test, which was explained before. These are the values shown in the results section.

V. FC analysis

The FC statistical analysis was based as well in the methodology introduced by Maris and Oostenveld (Maris & Oostenveld, 2007). The procedure was carried out independently for each frequency band. First, an exploratory t-test was calculated per each PLV value. Then, those channels with at least two significant links were taken into account as members the significant network. These PLV values were submitted to the nonparametric test explained before. The last step and similarly to the power analysis procedure, we calculated another t-test between groups with the averaged PLV value across each significant network. This comparison was checked via the nonparametric test and corresponds with the values shown in the results section.

In addition, Spearman correlation test in the BS sample was calculated between the significant average values (both PS and FC) and the BAC score. These scores were checked as well by means of corresponding nonparametric test.

Finally, the effect sizes of the significant results were calculated through the following expression:

$$\Delta = \frac{\overline{X_{BD}} - \overline{X_{CN}}}{\sigma_{CN}} \qquad [2.5]$$

where σ_{CN} was the standard deviation of the control group. The X_{BD} and X_{CN} values corresponded with the average significant value (PS or FC) of the BD and control group, respectively.

2.3. Results

2.3.1. Relative PS

The average relative power in the 1-45 Hz range was obtained for each group. We found differences only within the first third of the spectra, so only this section is depicted in figure 2-1. The profile of the spectral distribution was different for both groups. Both showed the maximum peak around 10 Hz frequency and significant differences between groups were found within two ranges. 1) A range within theta band that included frequencies between 4 Hz and 6 Hz (henceforth called theta range), with BD group displaying increased theta range power in an occipital cluster of sensors compared to the control group ($t = -2.014$, $p = 0.044$). 2) A range within alpha band that included frequencies between 9 Hz and 11 Hz (henceforth called alpha range), where the BD group showed reduced alpha range power in a temporal-occipital cluster of sensors as compared to the control group ($t = -2.294$, $p = 0.025$). The effects size values per the comparison of the average significant power of theta and alpha ranges are 0.64 and -0.51, respectively.

The possible gender influence was tested for all results through and extra two way ANOVA test with gender and group as main variables. Neither gender main effect nor gender by group interaction were found significant ($p > 0.05$).

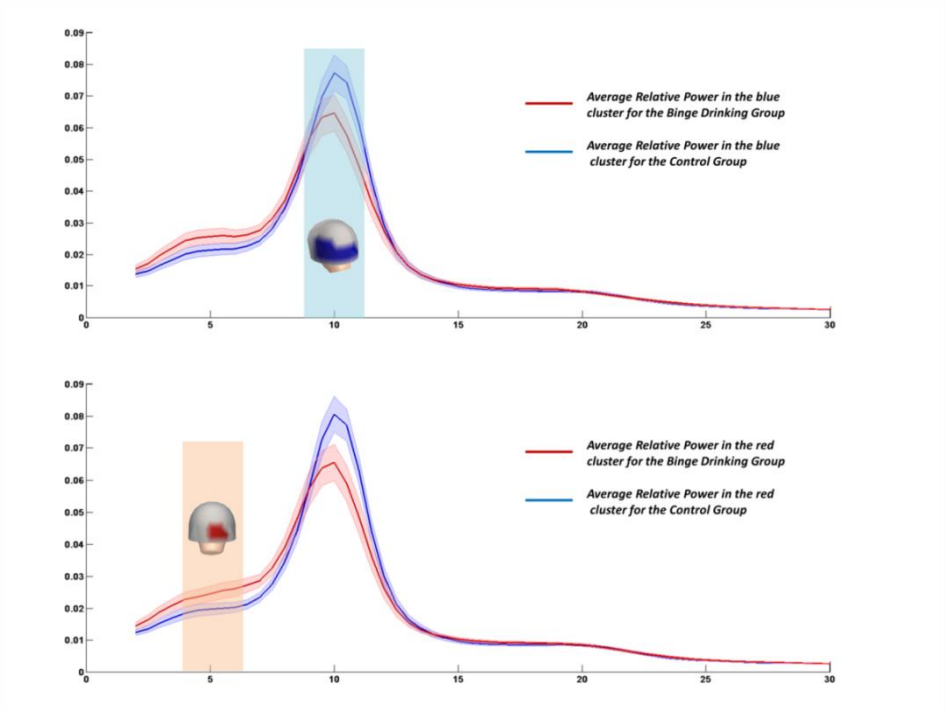

Figure 2-1 Power Spectra results.

Top, differences within the alpha band range [9-11Hz]. The cluster in blue color represents a decrease in relative power in the binge drinking group in temporo-occipital regions in comparison with the control group. Red and blue lines depicted the average relative power spectra for the channels of the blue cluster in the binge drinking group and control group, respectively. Highlighted region in blue refers to the frequency range with significant differences in the blue cluster of channels. Bottom, differences within the theta band range [4-6Hz]. The cluster in red color represents an increase in relative power in the binge drinking group in the occipital region in comparison with the control group. Red and blue lines depicted the average relative power spectra for the channels of the red cluster in the binge drinking group and control group, respectively.

2.3.2.Functional connectivity

Regarding FC, significant differences were found in delta, theta, alpha and beta bands. In delta, theta and beta the FC of the BD group was enhanced compared with the FC of the control group, whilst in alpha band the BD group showed diminished FC.

In delta band, a hyper-synchronized network in the BD group was located by connecting the right frontal and right temporal areas ($t = -3.3883$, $p = 0.0012$). When the FC in theta band was analyzed, a network connecting the middle frontal and the middle parietal areas showed increased FC in the BD group relative to the control group ($t = -2.8471$, $p = 0.0058$). Another network with enhanced FC was found in beta band, where an increased long range FC was found in the BD group between right frontal and right temporal regions ($t = -3.6786$, $p = 0.0005$). Finally, the FC analysis in alpha band showed diminished synchronization in the BD group in a long range network, which connected the left frontal and left temporal areas ($t = 2.8585$, $p = 0.0056$) (see Figure 2-2). Significant values of FC in alpha band correlated negatively with the BAC value of the BD group ($rho = -0.56$, $p = 0.00088$), therefore, the more BAC value, the less alpha FC between the left frontal and the left temporal areas.

The effect size values per the comparison of the average significant FC delta, theta alpha and beta bands are 0.64, 6.69, -0.65 and 0.87 respectively.

The possible gender influence was tested for all results through an extra two way ANOVA test with gender and group as main variables. Neither gender main effect nor gender by group interaction were found significant ($p < 0.05$).

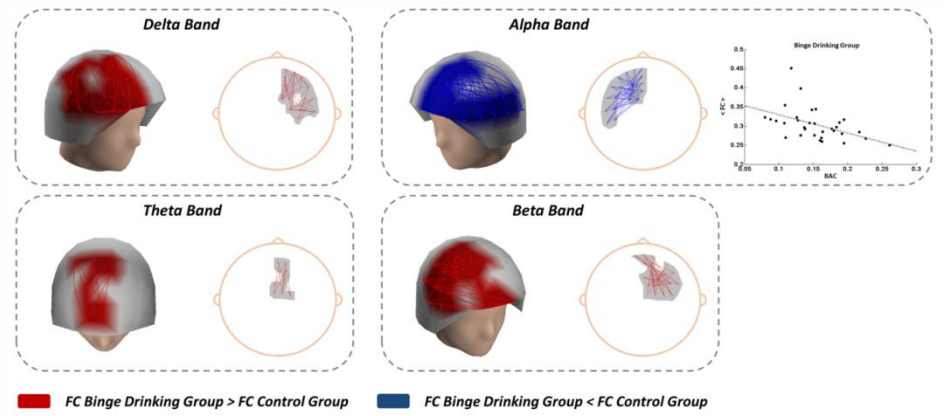

Figure 2-2 Functional Connectivity results.
This figure shows the significant network for each frequency band. 3D and 2D model show the same networks. The FC of the control group is employed as the reference and a line between two channels represents a link whose FC value has been found significantly different between both groups. The red/blue color indicates that the FC of the BD group has been found enhanced/diminished in comparison to the FC of the control group. The effects sizes values per comparison of the average FC of the delta, theta, alpha and beta significant networks are 0.64, 0.69, -0.65 and 0.87, respectively. For alpha band, the scatter plot depicts the significant Spearman correlation between the average FC of the alpha significant network and the BAC score in the BD population (rho = -0.56, p =0.0002).

2.4. Conclusions

This is the first study assessing brain magnetic activity of young binge drinkers. The results of the present study showed that FC and PS, as assessed by MEG signal during eyes-closed resting state, differ between young control and BD students. The statistical analysis indicated that: 1) the BD group, compared to the control group, depicted diminished PS in alpha and enhanced in theta frequency ranges in occipital areas; 2) FC analysis showed a significant increase in the BD group in delta, and beta bands in right fronto-temporal networks, and also in the theta band in a middle fronto-parietal network, together with a significant decrease in alpha synchronicity between left

frontal and parietal regions. Furthermore, alpha FC correlates negatively with the estimated BAC, leading support to the idea that the psychophysiological differences of this population may be consequence of increased levels of alcohol consumption.

3. EXPERIMENTAL STUDY II

Functional and Structural Connectivity of Young Binge Drinkers: a Follow-up Study

3.1. Aims and hypothesis

The aim of the present study is to evaluate the evolution of the functional and anatomical connectivity of the Default Mode Network in young binge drinkers along two years period. Magnetoencephalography signal during eyes closed resting state as Diffusion Tensor Imaging were acquired twice within a 2-year interval from 39 undergraduate students (22 controls, 17 binge drinkers) with neither personal nor family history of alcoholism. In this study we tested the hypothesis that a continued pattern of a binge drinking of alcohol consumption may lead to functional anomalies in the normal brain maturation process.

3.2. Methods

3.2.1. Participants

Thirty-nine undergraduate students of the Complutense University of Madrid (Madrid, Spain) participated in the study. Twenty two were classified as controls (12 females) and 17 as BDs (8 females). The procedure for subject selection is fully described in Correas et al. (Correas et al., 2015). The participants were evaluated twice within a 2-year interval (at 18-19 and 20-21 years old) and the number of months between evaluations of each group didn't differ (control group = 22.86±0.89; BD group = 23.26±0.94). The demographic data of each group is shown in Table 1.

Participants were divided into BD and control group according to a questionnaire and a semi-structured interview inquiring about alcohol and other drug consumptions habits. Participants were asked to cover a record of daily consumption indicating what they drank, the quantity and for how long (hours). The BAC was calculated based on the information of the last dinking episode. We considered the BAC as a rough index representing the BD level of each subject. Participants reaching a BAC of 0.08% or above at least once during the last month were classified as BD. On the other hand, the control group consisted of students who never achieved that BAC. All volunteers provided written informed consent prior to assessment. Participants were asked to refrain from alcohol consumption for, at least, 24 hours prior to MEG recordings. Subjects were submitted to a breathalyzer test, and the assessment was only performed after verifying a 0.00% breath alcohol level.

Table 3-1 Demographic, tobacco and alcohol consumption data.

	First evaluation		***Second evaluation***	
	Controls	***Binge Drinkers***	***Controls***	***Binge Drinkers***
N (females)	22(12)	17(8)	-	-
Age	18-19	18-19	20-21	20-21
Handedness (right/left)	22/0	17/0	-	-
Caucasian (%)	100	100	-	-
Tobacco use	0	3	0	3
BAC	0.016±0.024	0.166±0.065	0.017±0.029	0.152±0.052

*BAC (Blood Alcohol Concentration): grams of alcohol in a BD day, mean±SD.

3.2.2.MEG Acquisition

Four minutes of MEG signal were acquired (1000 Hz sampling rate and online band pass filter at 0.1-330 Hz) during eyes-closed resting state using a 306-channel (102 magnetometers and 204 gradiometers) system (Elekta©, VectorView). In this study only magnetometers (102 channels) information was submitted to source and statistical analyses. The system was housed in a magnetically shielded room (VacuumSchmelze GmbH, Hanua, Germany). The head movement was monitored by means of four head-position indicator coils attached to the scalp. Ocular movements were tracked with two bipolar electrodes.

3.2.3.MEG analysis

Preprocessing

The raw recording data were at first submitted to Maxfilter software (v 2.2, Elekta Neuromag) to remove external noise with the temporal extension of the signal space separation method with movement compensation (Taulu & Simola, 2006). In this study, we used only magnetometers data in order to avoid mixing MEG sensors with different sensitivities or resorting to scaling. Accordingly, all of the magnetometers' resting state signals were automatically scanned for ocular, muscle and jump artifacts with Fieldtrip package (Oostenveld et al., 2011) and were visually confirmed by a MEG expert. The artifact-free data were segmented in continuous 4 seconds fragments (trials). At least 15 clean trials (60 seconds of brain activity) were obtained from all participants and preserved for further analyses. The number of surviving trials did not differ significantly between groups. To calculate the source´s reconstruction, the time series were filtered in the following frequency bands: delta (2-3.9 Hz), theta (4.1-7.9 Hz) alpha (8.1-11.9 Hz) and beta (12.1-29.9 Hz). The filtering was performed with a finite impulse response filter of order 1500. This filter was applied using a two-pass procedure over the whole four-minute registers, in order to avoid phase distortion and edge effects.

Headmodels & Beamforming

A regular grid of 2455 nodes with 1 cm spacing was created in the Montreal Neurological Institute (MNI) template brain. This set of nodes was transformed to each participant´s space using a non-linear normalization between the native T1 image (whose coordinate system was previously

converted to match the MEG coordinate system) and a standard T1 in MNI template space. The forward model was solved with the realistic single-shell model introduced by Nolte (Nolte, 2003).

Source reconstruction was performed with a Linearly Constrained Minimum Variance Beamformer (Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997). For each subject, the covariance matrix was first averaged over all trials to compute the spatial filter´s coefficients and these coefficients were applied to individual trials, obtaining a time series per segment and the source location.

Atlas Based Analysis

The FC analysis was performed using atlas-based ROIs. For the subsequent analysis, we specifically focused on FC in the DMN. We set DMN-related ROIs in the precuneus (Pc), posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), frontal medial cortex (FMC) and bilateral inferior parietal lobe (IPL) by referring to the Harvard-Oxford probabilistic (Desikan et al., 2006). In total, 156 nodes were included in this study as they were located within the 6 ROIs.

Functional Connectivity: Phase Locking Value

The FC was measured by means of phase-locking value (PLV) (Van Veen et al., 1997) in each frequency band and was calculated per each trial as explained in (Correas et al., 2015). Finally, the results were averaged across trials ending up with symmetrical 156 x 156 nodes connectivity matrices per subjects, phase (pre/post) and frequency band. In order to assess changes over time, we assess the ratio of change between the two phases of the longitudinal study by dividing the value of each connectivity node of the second evaluation between the first evaluation. Finally, to address whether volume conduction could be causing these differences, we have calculated the correlation between beamformer weights in both groups in order to have an estimate of volume conduction (Brookes et al., 2011). Beamformer weights did not differ between groups in any frequency band, which makes it unlikely that the functional connectivity differences were caused by volume conduction.

Statistical Analysis

Clusters of connections, which showed statistically significant group differences (BD subjects vs. control subjects), were explored relying on the cluster-based permutation test (Maris & Oostenveld, 2007) for each frequency band. The methodology was composed by two steps: 1) an intra-ROI analysis that computed the local connectivity within each ROI; and 2) inter ROI FC that evaluated the inter-regional FC among each pair of ROIS of the DMN. In both cases, the procedure was essentially the same. In the intra-ROI analysis, we assessed the FC of all the nodes contained within

a ROI; whereas in the inter-ROI the analysis we focused in the FC between the nodes located in the corresponding two bilateral ROIs.

The procedure started by assessing the FC difference between groups for each pair of nodes by means of ANCOVA with sex as a covariate. The significance of the links was assessed using a non-parametric randomization (5000 permutations) testing (Ernst, 2004). Only those links with p-values below 0.05 were kept and included in the following steps of the analysis. Then, we aimed to extract a robust significant network, so-called *network motifs* in graph theory (Cornelis J. Stam, 2014). These networks consisted of several consecutive significant links, which systematically showed a diminished or enhanced FC in the BD group compared with the CN group. We considered a significant motif only when: 1) at least the 25% of the nodes which composed the ROI were involved, 2) at least the 10% of the links among them had significant FC differences between groups, and 3) the motifs should be connected, i.e. there exists a path between each pair of nodes in the motif (C J Stam et al., 2014). The first two conditions set the minimum dimensions of the motif, and the third one fixed a constraint in the morphology, dismissing the insulated links. Then, we submitted all the FC values of the links that composed the significant motifs to a cluster-based (in this case motif-based) non-parametric test (5000 permutations) (Cuesta, Garcés, et al., 2014; Garcés et al., 2013) to control the multiple comparisons problem. At this point, we wanted to offer a value which would characterize the network of each significant cluster. Thus, we calculate for each significant motif their corresponding degree (Cornelis J. Stam, 2014), i.e. the average PLV-ratio across all links. Then we performed an ANCOVA with sex as covariate between groups, which was corrected by multiplying the *p* value by 5, to further account for the family-wise error for the 5 frequency bands, and we obtained the corresponding effect sizes (Cohen's d). In addition, we applied a classification analysis using a logistic regression analysis with the leave-one-out cross-validation procedure (Lopez et al., 2014). Finally, we performed a one-sample t-test to determine whether the value of the ratio of each group differs from a distribution with mean 1.

3.2.4.MRI Acquisition

MRI was collected from a General Electric 1.5 Tesla using an eight-channel head coil. The imaging protocol consisted of: 3D T1-weighted high-resolution images using a Fast Spoiled Gradient Echo sequence [TR/TE/TI=11.2/4.2/450 ms; flip-angle=12**°**; FoV=250 mm; acquisition matrix=256 x 256; slice thickness=1 mm] and Diffusion weighted Image (DWI) using a single-shot echo planar imaging sequence [TR/TE=12000/96.1 ms; FoV=307 mm; acquisition matrix=128x128; slice thickness=2.4 mm; NEX=3]. DWI was acquired along 25 non-coplanar directions with a b-value of 900 s/mm^2 and 1 image with no diffusion sensitization, i.e. b_0 image.

3.2.5.MRI analysis

DWI Analysis

DWIs were corrected for motion and eddy currents using EDDY-FSL, which performs linear affine registration of the volumes to the reference b_0 volume. The resulting rotations were used to realign the gradient directions matrix. Non-brain tissue was removed from DWI using BET-FSL and diffusion tensor images (DTIs) were obtained using a linear least-squares approach as implemented in FSL-FDT. From that several scalar images representing the shape of the diffusion tensor were obtained: fractional anisotropy, mean diffusivity, radial diffusivity and axial diffusivity.

Rigid transformations were performed between b_0 and T1-weighted images. In addition, linear affine transformations followed by nonlinear local deformations using FSL-FNIRT were applied to normalize brain-extracted T1-weighted images into the MNI brain template of 1 mm^3 isotropic resolution. These three transformations were concatenated in one single transformation in order to reduce the number of interpolations, and were applied inversely to transform the JHU white matter tractography atlas (Hua et al., 2008) into the diffusion subject-specific space. Average values for the different DTI metrics were obtained for each of the masks included in the JHU atlas.

Statistical Analysis

A repeated measures ANCOVA with sex as a covariate was performed with fractional anisotropy, mean diffusivity, radial diffusivity and axial diffusivity data.

3.3. Results

3.3.1. Functional connectivity

Results of the FC analysis are summarized in Table 2 and Figures 1 and 2. We did not found any significant difference between groups in the intra-ROI (intra-Region of Interest) analysis. In the inter-ROI analysis, we found several significant differences ($p<0.05$) between groups in the delta, theta and beta frequency bands. In all cases, the BD group showed an increased FC ratio when compared to the CN group. Besides from the group's comparison, the FC ratios in the BD group were always significantly higher than 1, which implied an increment of the FC along time. By contrast, the CN group showed a stable or decrement FC ratio along time (FC ratio <1 in 8 links, and non-different from 1 in 3 links). Regarding the ANCOVA´s covariate, sex was not significant in any of the connectivity links.

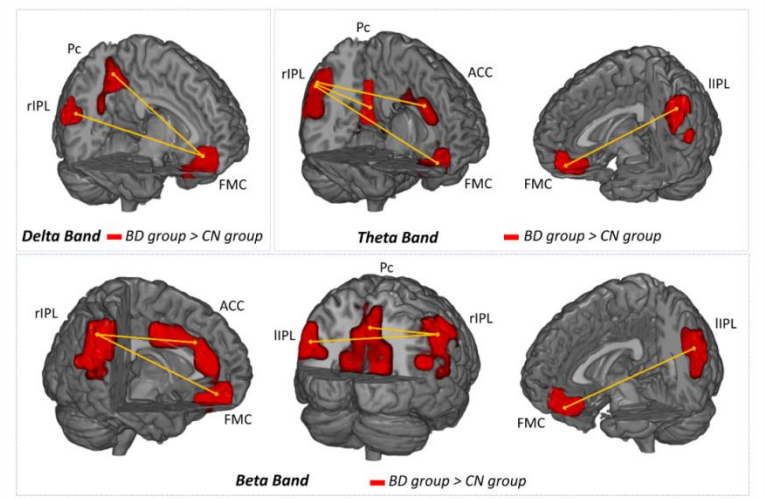

Figure 3-1 Significant differences of FC ratio between groups
The ROIs highlighted in red depict areas of the DMN with significant ($p<0.05$) enhanced FC ratio in the binge drinking group in comparison to the control group.

The significant FC network basically pointed out the existence of two kinds of FC patterns: 1) a frontal-parietal pattern, which involved mainly the FMC and its communication with both IPL and the Pc, and 2) a parietal pattern, which consisted of alterations in the communications between the rIPL and most of the DMN ROIs. The frontal-parietal pattern was found in delta, theta and beta frequency bands, whereas the parietal one emerged in theta and beta frequency bands.

Finally, the classification analysis pointed out that it is possible to distinguish between groups with a minimum and maximum of accuracy of 74% and 90% respectively (see Table 2).

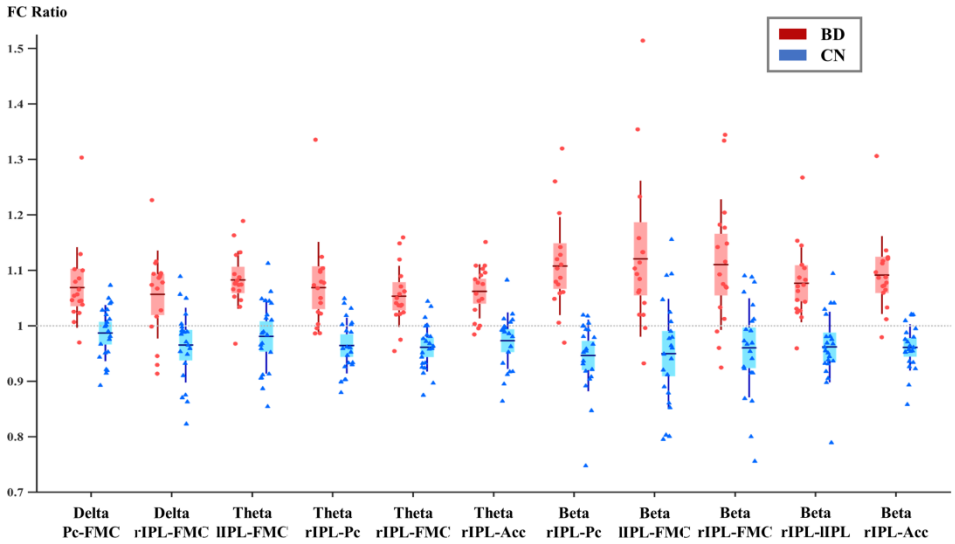

Figure 3-2 Functional Connectivity boxplot

The ratio value (post/pre) of each significant link and group are depicted. Red dots denote the ratio value of each subject of the binge drinking group (BD) and blue dots denote the ratio value of each subject of the control group (CN).

Table 3-2 Functional Connectivity results.

Band/Link	FC Ratio BD	FC Ratio CN	Effect Size	Ancova	Accuracy	T test BD	T test CN
Delta/FMC-Pc	1.07±0.07	0.99±0.05	Δ = 1.7	***p < 2e-04**	74%	***p < 1e-03**	p < 2e-01
Delta/FMC-rIPL	1.06±0.08	0.97±0.07	Δ = 1.4	***p < 5e-04**	79%	***p < 9e-03**	***p < 3e-02**
Theta/lIPL-FMC	1.08±0.05	0.98±0.07	Δ = 1.5	***p < 6e-06**	79%	***p < 5e-06**	p < 2e-01
Theta/rIPL-FMC	1.05±0.06	0.96±0.04	Δ = 2.2	***p < 7e-07**	87%	***p < 3e-03**	***p < 2e-03**
Theta/rIPL-Acc	1.06±0.05	0.97±0.05	Δ = 1.8	***p < 3e-06**	85%	***p < 9e-04**	***p < 3e-04**
Theta/rIPL-Pc	1.07±0.08	0.96±0.05	Δ = 2.1	***p < 3e-05**	82%	***p < 6e-05**	***p < 2e-02**
Beta/lIPL-rIPL	1.08±0.07	0.96±0.06	Δ = 1.8	***p < 5e-06**	82%	***p < 1e-04**	***p < 7e-04**
Beta/lIPL-FMC	1.12±0.14	0.95±0.10	Δ = 1.7	***p < 6e-05**	77%	***p < 2e-03**	***p < 3e-02**
Beta/rIPL-FMC	1.11±0.12	0.96±0.09	Δ = 1.7	***p < 6e-05**	77%	***p < 1e-03**	p < 6e-02
Beta/rIPL-Acc	1.09±0.07	0.96±0.04	Δ = 3.2	***p < 2e-08**	87%	***p < 3e-04**	***p < 9e-03**
Beta/rIPL-Pc	1.11±0.09	0.95±0.06	Δ = 2.5	***p < 6e-08**	90%	***p < 5e-05**	***p < 2e-04**

The FC ratio was calculated by means of the quotient: post FC / pre FC. ANCOVA test, with sex as covariate, was calculated between groups with the corresponding average FC ratio. The accuracy score was obtained through a logistic regression analysis with the leave-one-out cross-validation procedure. MNI coordinates of the center of each ROI were calculated in the corresponding network. One sample t-test was calculated with the ratio value of each group per each significant link. rIPL/lIPL (right/left inferior parietal lobe). Pc (precuneus). FMC (frontal middle cortex). ACC (anterior cingulate cortex).

3.3.2.Structural Connectivity

As a result of repeated measures ANCOVA performed with DTI data, we did not find any group differences neither in the pre nor in the post condition. Likewise, no intragroup differences in the BD group were found across time.

3.4. Conclusions

This is the first study assessing functional connectivity (FC) along with structural connectivity (SC) in young BD subjects who maintained a pattern of intensive alcohol consumption for more than two years. The results of the present study showed that the FC of the DMN, as assessed with MEG, increased over time in young subjects with a BD pattern compared to the control group. Namely, the BD group showed a significant enhanced FC ratio in several links among DMN ROIs. On those significant ROIs, the FC ratios were always significantly higher than 1 in the BD group, whereas the FC ratios in the control group remained stable or lower than 1. On the other hand, the SC, as assessed by fractional anisotropy, medial diffusivity, radial diffusivity and axial diffusivity did not show significant differences neither between groups nor over time. These findings point out that a continued pattern of binge drinking lead to functional alterations in the normal brain maturation process, even before anatomical changes can be detected.

4. EXPERIMENTAL STUDY III

Oscillatory Spatial Profile of Young Binge Drinkers during an equiprobable Go/NoGo Task

4.1. Aims and hypothesis

It is well known that alcohol affects response inhibition and that youth is a critical period of neuromaturation where cognitive functions are still developing. The major aim of the present study was to examine brain magnetic activity during response execution in an equiprobable Go/NoGo task in young binge drinkers with no personal or family history of alcoholism. In the present study we tested the hypothesis that the binge drinking pattern of alcohol consumption may impair target detection and therefore, the oscillatory brain activation during the Go/NoGo task of the binge drinking group would be different from the control aged matched subjects.

4.2. Methods

4.2.1. Participants

Fifty-one students of the Complutense University of Madrid (Madrid, Spain) participated in the study. They were assigned to a binge drinking (BD) group (N = 25, 13 females) and a control group (N = 26, 14 females) based on a questionnaire and a semi-structured interview inquiring about their alcohol and other drug use. Participants provided a record of their daily alcohol consumption indicating the type(s) and the quantity of the beverage(s) they consumed in the past month as well as the length of time (in hours) it took them to imbibe these beverages (see Table 1). Their Blood Alcohol Concentration (BAC) was estimated based on the information they provided for the last month, as well as their gender and weight. All drinking occasions during which a BAC of 0.08% was reached were defined as heavy episodic (binge) drinking. Participants reporting a binge episode at least once during the previous month were classified as BD. Conversely, the control group comprised individuals who never achieved that alcohol concentration.

In order to minimize possible influence of a genetic predisposition for alcoholism, participants were questioned about their personal and family history of alcoholism and those with family history of alcohol abuse were excluded from the study. Individuals reporting personal history of psychiatric disorders (axis I and II) based on DSM-IV-TR criteria and psychopathological traits as assessed by the Symptom Checklist-90 Revised questionnaire (SCL-90-R) were also excluded. Subjects reported no neurological or other conditions that could affect their cognitive functioning and were not taking any medication at the time of the study.

All participants provided written informed consent prior to assessment and were monetarily reimbursed for their participation. They were asked to refrain from alcohol consumption for at least 24 hours prior to data acquisition.

Table 4-1 Demographic, drinking, personality and neuropsychological data

	Control group	*Binge drinking*	*T test (p-values)*

N (females)	26 (14)	25 (11)	0.76
Age	18±0.8	18±0.4	0.93
Estimated BAC	0.017±0.02	0.17±0.072	**0.021***
Months drinking	4.55±3.71	20.67±10.45	**0.001***
Onset age	16.6±1.01	14.92±1.08	0.74
Days drinking/month	2.85±1.7	4.84±2.56	0.17
SSS - total	16.29±3.5	21.48±3.53	0.12
SSS - TAS	5.76±2.66	7.58±2.35	0.18
SSS - DIS	2.48±1.22	5.17±1.58	0.104
SSS - ES	5.56±1.58	5.43±1.77	0.94
SSS - BS	2.54±1.81	3.17±1.19	**0.04***
BIS - total	38.87±10.6	44.38±11.5	0.74
BIS - emotional	14.42±3.81	12.84±3.95	0.69
BIS - Motor	14.77±6.55	12.96±5.53	0.88
BIS - Nonplanning	15±4.53	14.2±4.95	0.28
D2 - total	504.23±66.17	460.84±68.87	0.57
IGT - total gains	12.15±16.61	12±11.47	0.65
IGT - total losses	18.38±15.48	23.36±20.56	0.089

*BAC: Blood Alcohol Concentration of the last drinking episode; SSS: Sensation Seeking Scale; SSS - TAS: Thrill and Adventure Seeking; SSS - DIS: Disinhibition; SSS - ES: Experience Seeking; SSS - BS: Boredom Susceptibility; BIS: Barratt Impulsiveness Scale; D2: Test of attention; WAIS-III: Wechsler Adult Intelligence Scale-III; IGT: Iowa Gambling Task. Significance level is indicated as follows: *p < 0.05, **p < 0.01, ***p < 0.001. (mean±SD).*

4.2.2.Task

An equal probability Go/NoGo task was used to evaluate stimulus detection and response execution. The participants were instructed to fixate on a small cross located centrally on the screen. Squares or circles were presented for 100 ms with a stimulus onset asynchrony (SOA) of 1,100 ± 100 ms. The participants were asked to press a button in response to the Go trials (green circle and blue square) and not to respond to the NoGo trials (blue circle and green square), as shown in Figure 1. A total average of 450 trials was presented in two blocks in random order.

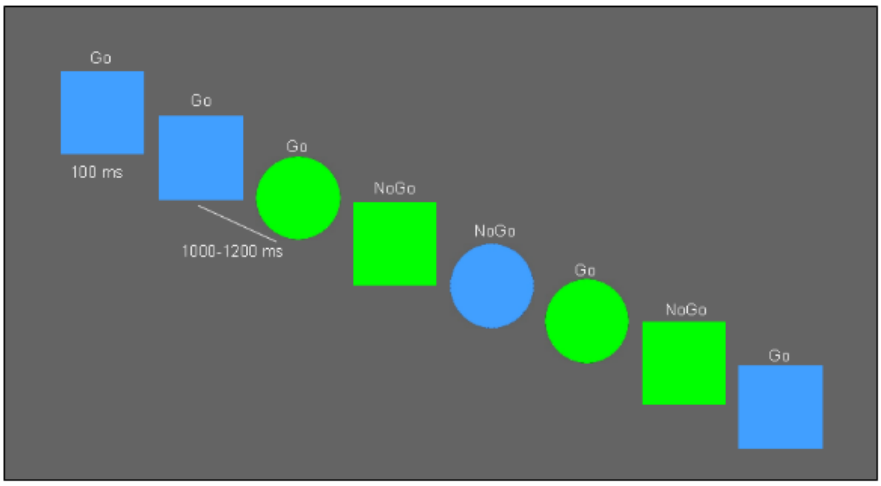

Figure 4-1 Equal probability Go/NoGo task representation

4.2.3.Data acquisition and analysis

MRI

Structural MRI images were acquired in order to define the model for the volume conductor and the solution space for MEG source localization analysis. Images were acquired with a General Electric 1.5 Tesla using an eight-channel head coil. The imaging protocol consisted of: 3D T1-weighted high-resolution images using a Fast Spoiled Gradient Echo sequence [TR/TE/TI=11.2/4.2/450 ms; flip-angle= 12°; FoV= 250 mm; acquisition matrix= 256 x 256; slice thickness=1 mm]. Structural images were used to reconstruct each person´s cortical surface with FreeSurfer software. Inner skull surface was derived from the segmented MRI data and used for a boundary element model of the volume conductor in the forward calculations. The solution space was approximated by ~5000 free-rotation dipoles along the gray-white matter surface in the cortex, with spacing between dipole locations ~7 mm.

MEG

High-density MEG signals were recorded from 204 channels (102 pairs of planar gradiometers) with a whole-head Neuromag Vectorview system (Elekta) in a magnetically and electrically shielded room. The signals were recorded continuously with a 1000 Hz sampling rate and were filtered online with a band pass filter 0.1-330 Hz. The position of magnetic coils attached to the skull, the main fiduciary points such as the nose, nasion and preauricular pints, as well as a large array of random points spread across the scalp were digitized with 3Space Isotrak II system for subsequent precise co-registration with structural MRI images. Trials with incorrect responses were excluded from all further analyses. In addition, the number of included trials was equated across task conditions (go and no-go) for each subject in order to eliminate potential bias due to

unequal number of trials. The MEG analysis stream primarily uses our custom Matlab functions and it relies partially on publicly available packages including FieldTrip (Oostenveld et al., 2011). Single trial MEG data were low-pass filtered at 100 Hz and epoched from -300 to 700 ms relative to stimulus onset for the stimulus-locked analysis. For each epoch, the data were downsampled by a factor of 4 to 250 Hz; linear trend was removed and mean activity across the entire epoch was subtracted from each time point. Epoched data were then passed through automatic threshold rejection to remove trials that were contaminated with artifacts. Independent component analysis was used to remove eye-blinks and heart artifact components (Delorme & Makeig, 2004). Complex power spectrum was calculated for each trial using convolution with complex Morlet wavelets (Lachaux et al., 1999) in 1 Hz increments from 4 to 7 Hz for theta band and in 2 Hz increments from 15 – 25 Hz (beta band). The first and last 300 ms of each epoch were discarded to remove edge artifacts potentially resulting from wavelet analysis. Theta and beta band power were plotted for each individual epoch to further visually inspect the wavelet results and reject additional artifact contaminated trials that had not been detected via the automatic threshold rejection procedure. To estimate the noise covariance for calculation of the inverse and to prevent biasing the inverse solution against spontaneous brain oscillations, we used empty room data that were detrended and band-pass filtered between 3 and 50 Hz. The signal-to-noise ratio (SNR) equaling 5 (Lin et al., 2004) was used for scaling of the noise covariance matrix in calculation of the inverse operator. The identity matrix was used for noise-sensitivity normalization of the source-space solution. The noise-sensitivity normalized estimates of total source power were obtained at each location on the cortical surface at each frequency. Estimated source power constrained to cortical surface was calculated based on the spectral dynamic statistical parametric mapping approach (Lin et al., 2004), by applying anatomically constrained MEG (aMEG) method based on cortically constrained minimum norm estimate (Dale et al., 2000) to the complex power spectrum. For each subject, a map of total source power for each band, theta and beta, was estimated by averaging across theta band frequencies (4-7 Hz) and beta band frequencies (15-25 Hz), and across all trials for each condition. Finally, total event-related theta and beta power were baseline-corrected by subtracting the mean theta and beta source power estimate in the 300 ms prestimulus period and expressed as percent signal change from baseline. Intersubject averages were created by morphing each subject´s reconstructed surface onto an average representation after aligning their cortical sulcar-gyral patterns (Fischl, Sereno, Tootell, & Dale, 1999) and averaging individual source power estimates.

Region-of-interest (ROI) analysis was conducted to further examine possible interactions of task condition, group and gender on event-related changes in theta and beta power. Unbiased ROIs

were selected based on the overall group average across all subjects for each task condition and comprised dipole locations along cortical surface with most notable source power. The same set of group-based ROIs was used for all subjects in a manner blind to their individual activations by applying an automatic spherical morphing procedure (Fischl et al., 1999). The ROIs primarily encompassed ventrolateral prefrontal cortex and motor cortex as shown Figures 1 and 2.

Mixed design ANOVAs were performed for each ROI and each frequency band with between-group factors of group (BD, Control) and gender, and a within-subject factor of Task condition (Go, NoGo) within the time window of 460-560 ms. Since no significant effects of Gender were observed in any of the analyses, reported are the results of the ANOVA with factors Condition and Group.

4.3. Results

4.3.1. Behavioral performance

Behavioral performance was assessed by measuring accuracy (% correct Go responses and % correct NoGo no-responses) and reactions times (RTs). Behavioral results are summarized in Table 2. There were no significant differences between the control and the BD group, or between genders, for any of the variables.

Table 4-2 Behavioral data for both groups

Behavioral Performance	*Controls*	*Binge Drinkers*	*T test comparison*
Responses Time (ms)	509.08±73.61	531.46±74.32	t (49)= 2.01 n.s
% correct Go	94.59±4.58	92.01±5.41	t (49)= 1.84 n.s
% correct NoGo	88.66±7.8	86.76±9.14	t (49)= 0.79 n.s

n.s.: not significant

4.3.2. MEG

For both theta and beta frequency bands, the group differences were mainly lateralized to the right hemisphere, peaking in the 450-550 ms time window as can be seen in figure 4-2 and the table 4-3.

Theta band (4-7 Hz)

The Go and the NoGo task conditions evoked different patterns of spatiotemporal activity as shown in figure 2. Both the motor (Mot) and the ventrolateral prefrontal areas (vlPFC) were sensitive to task condition with the correct target detection evoking greater event-related theta power than the NoGo trial in both groups. The main effect of group was significant in the right vlPFC area and the right mot area but it was due to group differences on the Go condition. In addition, the right and left vlPFC areas showed also significance in the interaction Condition X Group. Finally, for the Go condition the theta power of the BD group was reduced compared to the control group in the right and left vlPFC and in the right mot.

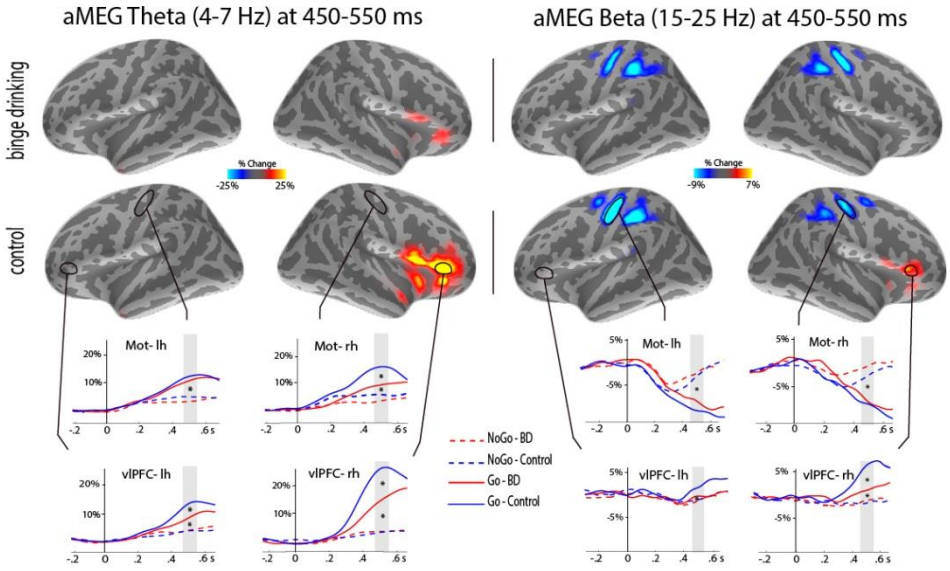

Figure 4-2 Group average maps and time courses.
Event-related theta and beta source power estimated to the lateral cortical surface. In both trial conditions (Go/NoGo) theta and beta activity at 450-550 ms is estimated to the motor (Mot) and ventrolateral (vlPFC) cortex.

Beta band (15-25 Hz)

In beta band, the Go and the NoGo task conditions also evoked different patterns of spatiotemporal activity as shown Fig 2. It is well-established that beta power decreases due to voluntary movement over sensorimotor areas (Pfurtscheller & Lopes da Silva, 1999). As expected, reduced movement-related beta power was observed to the Go condition in the sensorimotor area. There was no group difference in beta power decrease in this area. In contrast, in the ventrolateral prefrontal area (vlPFC), beta power increased during correct target detection (Go trials). There is no main effect of group in the Mot or in the vlPFC areas. A significant interaction between the Condition X Group factors was observed in the vlPFC. Event-related beta power increase on Go trials was greater in the control group compared to BD.

Table 4-3 MEG Theta and Beta Results (450-550 ms).

MEG Theta Results	*Condition, F(3,47)*	*Group, F(3,47)*	*Condition x Group, F(3,47)*	*Go- group, F(3,47)*	*NoGo- group, F(3,47)*
Right vlPFC	**42.84*** **	**5.01***	**5.55***	**4.76***	0.1
Left vlPFC	**26.49*** **	3.88	**4.83***	**5.01***	0.12
Right Mot	**22.71*** **	**4.78***	2.61	**4.13***	2.12
Left Mot	**29.31*** **	0.89	0.02	0.37	1.65
MEG Beta Results					
Right vlPFC	**16.65** **	3.4	**5.14***	**4.72***	0.47
Left vlPFC	**4.74** **	1.75	2.99	3.08	0.07
Right Mot	**27.42*** **	0.36	0.28	0.04	1.39
Left Mot	**35.19*** **	0.11	0.21	0.19	0.01

For each hemisphere, included here are the results for the main effects and interactions of group and task condition, as well as the simple main effects of group under Go and NoGo conditions. Significance level is indicated as follows: *p < 0.05, **p < 0.01, ***p < 0.001. Results are expressed as F-values.

Theta Correlations

The Go condition theta power of the right and left vlPFC positively correlated with the % of corrects responses (Go) r= 0.36, $p < 0.05$ (right vlPFC); r= 0.29, $p < 0.05$ (left vlPFC) and the D2 attentional test score r= 0.29, $p < 0.05$ (right vlPFC); r= 0.37, $p < 0.05$ (left vlPFC). Besides, the right vlPFC theta power negatively correlated with the BAC index r= -0.46, $p < 0.05$ and the left vlPFC negatively correlated with the Barratt Impulsivity Scale r=-0.32, $p < 0.05$.

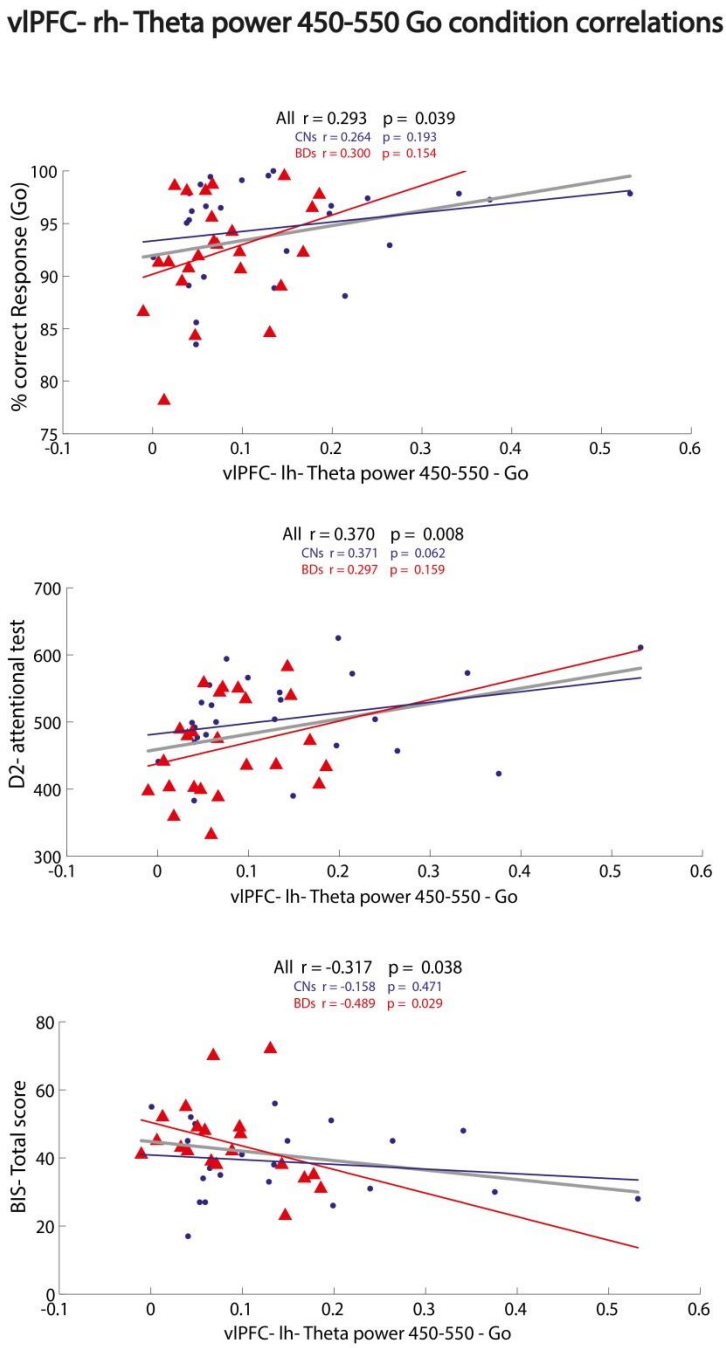

Figure 4-3 Correlation scatter plot (right hemisphere)
Scatter plots of the correlations between the right vlPFC theta power of the Go condition and the % of correct responses (Go), D2 attentional test score and the Barratt Impulsiveness Scale. Red triangle: Binge drinker, blue circle: healthy control.

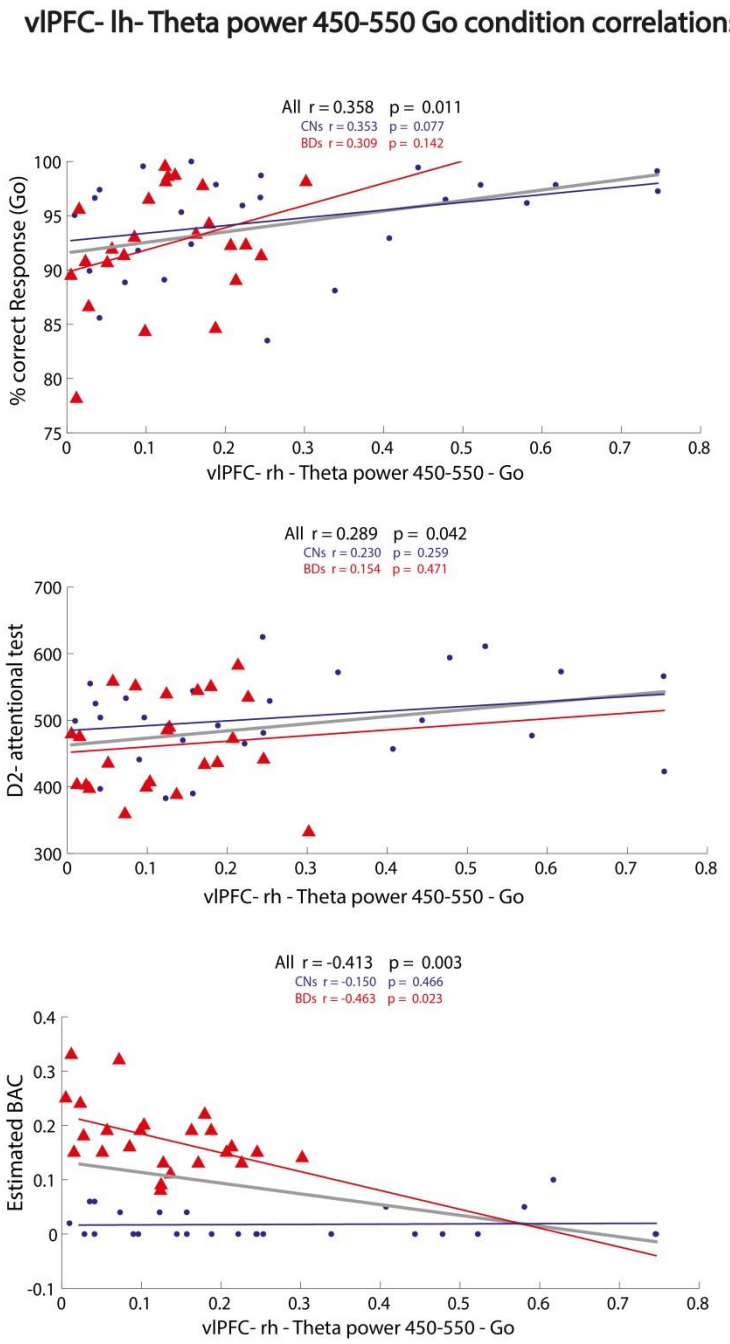

Figure 4-4 Correlation scatter plot (left hemisphere)
Scatter plot of the correlations between the left vlPFC theta power of the GO condition and the % of correct responses (Go), D2 attentional test score and the estimated Blood Alcohol Concentration. Red triangle: Binge drinker, blue circle: healthy control.

4.4. Conclusions

This study has employed a time-sensitive multimodal imaging approach to examine the effects of binge drinking pattern on event-related theta and beta power as a function of target detection in an equiprobable Go/NoGo task. The main findings can be summarized as follows: 1) the Go and the NoGo conditions evoked different patterns of activity with greater power evoked by Go trials in both bands overall. 2) In theta band, event-related power on Go trials was lower in BD compared to the control group in the vlPFC bilaterally and the right motor area. 3) In beta band, the power on Go trials was also lower in BD group in the right vlPFC. 4) Theta band power in the vlPFC bilaterally correlates with performance accuracy and attention. Furthermore, theta power correlates negatively with the estimated BAC in the right vlPFC and with self-reported impulsivity in the left vlPFC. Overall, these results indicate that binge drinking is associated with deficient activation in theta and beta frequency bands during target detection. These effects are especially prominent in the vlPFC and in the right sensorimotor cortex, suggesting impairments in target detection and response execution. Positive correlations between vlPFC theta power and selective attention point to an important role of attentional resources that may underlie these effects. Furthermore, theta in vlPFC correlates negatively with estimated intoxication levels and with impulsivity, lending support to the idea that cognitive deficits in binge drinkers may be a consequence of increased levels of alcohol consumption that are additionally modulated by impulsivity traits.

5. GENERAL DISCUSSION

The present dissertation has tried to determine whether the *binge drinking* pattern of alcohol consumption is associated with cerebral anomalies compared with healthy aged matched controls. To that end, we studied the brain magnetic activity (during resting state and the performing of an equiprobable Go/NoGo task) as well as the structural connectivity of this population. As far as we know, there are no previous studies on binge drinking and Magnetoencephalography which gives novelty to the present findings.

The principal scientific contribution made by this doctoral thesis is that we can affirm, by means of the three studies conducted, the existence of electrophysiological differences between young binge drinkers and young controls in their brain magnetic activity profiles. As it has been described in the corresponding section of each study, it is important to note that these electrophysiological differences were found in the absence of neurostructural differences (Study II) and cognitive differences (Study III). These facts can have two implications; first, the MEG has enough sensitivity to detect abnormalities in brain activity even before the presence of structural anomalies and second, before the existence of cognitive differences that clinical neuropsychological test can appreciate. This discrepancy between behavioral and psychophysiological results is not surprising given that the MEG can study brain activity with high temporal resolution and detect physiological abnormalities that may not be apparent on cognitive performance.

Below, I will detail and discuss the results found in the three studies conducted in the present dissertation in relation to the aims and hypothesis established above.

5.1. **Experimental Study I:** *Exploratory analysis of Power Spectrum and Functional Connectivity during Resting State in Young Binge Drinkers*

This is the first study assessing brain magnetic activity of young binge drinkers. The results revealed that FC and PS, as assessed by MEG signal during eyes-closed resting state, differ between young control and BD students. The statistical analysis indicated that: 1) the BD group, compared to the control group, depicted diminished PS in alpha and enhanced in theta frequency ranges in occipital areas; 2) FC analysis showed a significant increase in the BD group in delta, and beta bands in right fronto-temporal networks, and also in the theta band in a middle fronto-parietal network, together with a significant decrease in alpha synchronicity between left frontal and parietal regions. Furthermore, alpha FC correlates negatively with the estimated BAC, lending support to the idea that the psychophysiological differences of this population may be consequence of increased levels of alcohol consumption.

5.1.1. PS differences

Given that several studies evaluating PS during resting state in alcoholics have also found an increase in theta (Rangaswamy et al., 2003) as well as a decrease in alpha (Porjesz et al., 2005a; Saletu-Zyhlarz, 2004) band, our results seem to indicate that the BDs might exhibit a similar spectral pattern as alcoholics in these frequency bands.

Regarding theta band, it is known that this frequency band decreases across individual development (Gómez, Pérez-Macías, Poza, Fernández, & Hornero, 2013; Niedermeyer, 2005). In the same way, reductions in PS of theta bands have been related to the reduction that naturally occurs in the cerebral gray matter volume from childhood to young adulthood (Whitford et al., 2007). In the same line as previous studies have associated the BD pattern of alcohol consumption in youths with a potential neuromaturational delay, i.e., with greater grey matter volumes in certain cortical and subcortical regions due to a lower synaptic pruning (Doallo et al., 2014; Howell et al., 2013; Squeglia et al., 2012), the greater theta band observed in BDs could be related with a neurodevelopmental delay in these subjects. However, this interpretation is still tentative and new studies assessing PS and cortical thickness are necessary to test this hypothesis.

Regarding alpha band, there is considerable evidence stating that the resting state eyes-closed condition induces an oscillatory activity around 10 Hz over the posterior scalp regions in healthy subjects (Schürmann & Başar, 2001). Besides, large alpha power in a resting state period has been related to good memory performance during a memory task (W. Klimesch, 1997; Wolfgang Klimesch, Doppelmayr, & Hanslmayr, 2006). Thus, the decrease in alpha band in occipital areas of the BD group may be related to a deficit in memory compatible with cognitive studies with this

population showing deficits in memory tasks (Mota et al., 2013; Parada, Corral, Caamaño-Isorna, Mota, Crego, Holguín, et al., 2011; Sneider et al., 2013).

A recent study has shown that acute alcohol intoxication also affects alpha band, increasing its short-term power mainly during eye-closed resting state, also measured by MEG (Rosen et al., 2014). Therefore, it would be possible that a consumption pattern which includes repeated alcohol intoxication, as BD, could affect long-term PS, specifically to alpha band power.

To our knowledge, only one previous study has evaluated PS in BDs. In this EEG study, Courtney and Polich (2010) found differences in PS between university students who varied in their alcohol consumption (Courtney & Polich, 2010). High-binge drinkers (> 10 drinks in under two hours on more than one occasion within the past six months) exhibited increased PS in the delta and fast-beta (20-35 Hz) bands as compared to non- and low-binge drinkers (5/4-7/6 drinks under two hours). However, there were no differences between non-binge drinkers and low-binge drinkers in these frequency bands. In our study, controls (light drinkers) and BD subjects display similar patterns of alcohol consumption as the non- and low-BDs observed in the Courtney and Polich's study. It must be noted that our BD sample is equivalent to the low-BD group in that study. Thus, the absence of differences in the delta and fast-beta frequency ranges of our study is consistent with the results presented by these authors. On the other hand, we do find PS differences between our groups, unlike the absence of differences between non- and low-binge drinkers in their study. The divergence between both results might be due to the differences between the two studies: EEG vs. MEG recording, eyes-open (EO) vs. eyes closed (EC) resting state, or the number of subjects in the sample. PS significant differences found in this study were mainly located in occipital MEG sensors, typical areas where alpha is activated during resting state. Differently, Courtney and Polich´s EEG differences were found in the Cz electrode. Another difference between studies is that PS of resting state EC varies form EO and also its spatial distribution. The major difference between conditions is the reduction of alpha band from EC resting state to EO (Chen, Feng, Zhao, Yin, & Wang, 2008). New EEG and MEG recordings will be necessary to clarify the alteration patterns during resting state in young people with a BD pattern of alcohol consumption.

5.1.2.FC differences

As stated in the introduction section, the loss of white matter integrity associated may entail a lower efficiency in the communications among brain regions and therefore, we think that it may

affect the FC and the PS. In this sense, several studies using fMRI have observed disturbances in FC in alcoholic patients during resting state (Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011) as well as during performance of different cognitive task (Courtney, Ghahremani, & Ray, 2013; Lee et al., 2013; Park et al., 2010; Rogers, Parks, Nickel, Katwal, & Martin, 2012). Another study conducted by Bruin and cols. (2006) showed impaired synchronization of the brain activity (reflected as lower alpha and slow-beta activity in the EEG) during resting state in a population of adults heavy drinkers, whose alcohol consumption was between 21 and 53 drinks per week (de Bruin, Stam, Bijl, Verbaten, & Kenemans, 2006). However, in this study the main result involved a heavy and regular drinker population, which does not match with our sample of BDs.

While these studies in subjects with alcohol dependence or abuse report impairments in neural networks, it is still questioned whether BD could cause connectivity disruption. In this sense, as stated in the introduction section, two studies from the same laboratory observed that white matter integrity was also compromised in young BDs in several association and projection white matter tracts, such as occipital and fronto-temporal connections (J Jacobus et al., 2009; McQueeny et al., 2009). Altered white matter integrity could partially underlie functional alterations in BD population observed in these regions. To our knowledge, no study has evaluated the FC networks in this population during resting state. Only one study examined the brain FC in young subjects (aged 22-27 years) with a pattern of consumption of 30 or more alcoholic drinks per week during resting eyes closed state (de Bruin et al., 2004). This regular and heavy alcohol consumption, although different from the BD pattern, seems to induce FC disruptions partially similar to those observed in the BD group of our study. In that study, the heavy alcohol drinkers displayed higher synchronization in theta and gamma bands as compared to the control group. The augmented theta synchronization in these heavily drinking students resembles the increased theta FC in the BDs students of our study.

Our results also showed a diminished synchronization between left frontal and left temporal areas in the BD group. As stated above, alpha rhythm is the most dominant in resting state, and is strongly related with several cognition processes (del Río et al., 2012; W Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998; W Klimesch, 1999), and has an important functional role in the inhibitory processes (Jensen & Mazaheri, 2010; Wolfgang Klimesch, Sauseng, & Hanslmayr, 2007; Scheeringa, Petersson, Kleinschmidt, Jensen, & Bastiaansen, 2012). There is growing evidence about the importance of the fronto-parietal regions in efficient cognitive control (Petrides, 2005; Seeley et al., 2007). But more important seems to be the interaction of alpha rhythm with those brain regions which are suppressed during cognitive control task (Buckner et

al., 2008). This interaction, consisting in a switch between externally and internally oriented cognition is really important for cognitive performance (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010), even in resting state (Fox et al., 2005). So the inhibition role of alpha band could be an effective mechanism to regulate the output of cortical networks (Jensen, Bonnefond, & VanRullen, 2012). Several studies have found that BD adolescents perform poorly in task involving prefrontal activity (García-Moreno et al., 2008; Scaife & Duka, 2009) and especially in inhibitory control processes (Nederkoorn, Baltus, Guerrieri, & Wiers, 2009a; Townshend & Duka, 2005). In this sense, the diminished FC of the BD group in alpha band involving left frontal and temporal areas at rest found at this study could represent a sing of neural anomaly accountable for the poor performance in inhibition might increase impulsivity contributing to the development, persistence and/or severity of AUD (Fulton Timm Crews & Boettiger, 2009; Meule, Lutz, Vögele, & Kübler, 2014).

Furthermore, another proof that reinforces the fact that the BD pattern produces a FC decrease in alpha band is the negative correlation found between this decline and the increase of the BAC score, therefore the more the BAC the less the alpha FC between the left frontal and the left temporal areas.

Regarding the increased FC in delta, theta and beta bands, enhanced FC has also been observed in several abusing groups of substances, such as alcohol, opioids or cannabis (Camchong, Stenger, & Fein, 2013; Coullaut-Valera et al., 2014; Fingelkurts et al., 2006; Kaplan, Glueck, Hesselbrock, & Reed, 1985; Orr et al., 2013). This increased FC has often been interpreted as a compensatory mechanism for the reduced or altered FC in other regions. Other studies with adolescent and young students have concluded that BD pattern can lead to a neural over-activation, in spite of the absence of behavioral performance differences (Campanella et al., 2013; Eduardo López-Caneda et al., 2012, 2013; Alecia D Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010b). This neural hyperactivity has also been explained as compensatory cerebral changes in order to facilitate normal behavior performance. Thus, it is possible to think that the increased FC in delta, theta and beta bands might result from a compensation of the decrease of alpha band, but we are not able to validate it without further neuropsychological information.

In summary, this is the first study assessing FC and PS profiles measured with MEG in young BD. The differences found in this study between BDs and controls could represent an initial sign of an abnormal oscillatory and synchronized neural activity associated to alcohol consumption. The high prevalence of this behavior among young population increases the necessity of further studies in order to confirm the results and clarify the dimension of this problem.

5.2. Experimental Study II: *Functional and Structural Connectivity of Young Binge Drinkers: a Follow-up Study*

This is the first study assessing functional connectivity (FC) along with structural connectivity (SC) in young BD subjects who maintained a pattern of intensive alcohol consumption for more than two years. The results of the present study showed that the FC of the DMN, as assessed with MEG, increased over time in young subjects with a BD pattern compared to the control group. Namely, the BD group showed a significant enhanced FC ratio in several links among DMN ROIs. On those significant ROIs, the FC ratios were always significantly higher than 1 in the BD group, whereas the FC ratios in the control group remained stable or lower than 1. On the other hand, the SC, as assessed by fractional anisotropy, medial diffusivity, radial diffusivity and axial diffusivity did not show significant differences neither between groups nor over time.

To the best of our knowledge, only one study has examined the brain FC in young binge drinkers during resting state. That previous study, carried out by our research group (Correas et al., 2015), was conducted when the age of the subjects was 18-19 and we found that the BD group already showed an increased FC in the delta, theta and beta frequency bands in frontal areas, as well as a decreased FC in the alpha band. In the present follow-up study, we have analyzed the rate of change of each group over two years and noticed that the BD group has increased its DMN FC over time in delta, theta and beta frequency bands. By contrast, a decrease of FC of some links of the DMN was observed in the control group. Given the longitudinal nature of the current study, it is important to consider this decrement of FC in the control group in the context of typical adolescent neural maturation. During brain maturation, adolescents exhibit less activation over time, as neural networks become more developed and efficient (Luna et al., 2010). As it can be seen in the present results, the typical pattern of neural maturation occur among adolescents who remained nondrinkers, but in the case of young people who continued drinking over those two years, the opposite pattern occurred. These results suggest that alcohol consumption may alter the typical neural development and may produce a developmental delay, hypotheses reported by different studies on binge drinking (Doallo et al., 2014; Howell et al., 2013; Joanna Jacobus & Tapert, 2013; Eduardo López-Caneda, Mota, et al., 2014; Squeglia et al., 2012).

In this line, this relative brain immaturity might be related to the effects of alcohol on brain receptors. It is well established that moderate to heavy alcohol intake disrupts the normal functioning of brain receptors, mainly N-methyl D-aspartate (NMDA) and gamma-aminobutyric acid-A ($GABA_A$) (Tsai & Coyle, 1998; Ward, Lallemand, & de Witte). Given that glutamate-sensitive NMDA receptors has a central role in the synaptic pruning needed to remove and strengthen brain connections (Stoneham, Sanders, Sanyal, & Dumas, 2010), it is possible that a BD pattern during adolescence may interfere with the cortical networks refinement mediated via NMDA receptors. In

accordance with this argument, several studies with structural MRI have reported greater grey matter volume in BDs compared to controls in cortical (Doallo et al., 2014; Squeglia et al., 2012) and subcortical regions (Howell et al., 2013). On the basis of these findings, it has been proposed that this enlarged cortical and subcortical volume would be cause by the reduced pruning resulting from excessive alcohol consumption. Together, these impairments in brain development could explain the opposite pattern of change in the FC of BDs as compared to controls (increase vs. decrease of the DMN FC) observed in the present study.

On the other hand, fMRI studies have also found increased brain activity in the BD subjects during the performance of different cognitive tasks such as verbal learning (Alecia D Schweinsburg et al., 2010a), working memory (Squeglia et al., 2011) and decision making (Xiao et al., 2013). This increased brain activity in the BD group, despite having the same behavioral performance, has been interpreted as a compensatory mechanism that allows maintaining an equivalent cognitive performance level. The results of these fMRI studies are no directly comparable with those obtained in the present work, since the BOLD activity obtained with fMRI is different from the FC obtained with MEG, and also the brain networks involved in performing a cognitive task are different from the DMN. However, our results can be added to the existing studies which have found brain hyperactivity in BD population. In a recent study, Wetherill et al. (Wetherill et al., 2013) found, in a longitudinal study, that future heavy drinkers showed higher brain activation during response inhibition than nondrinkers after transitioning into heavy drinkers. Similarly, previous EEG studies from our research group showed that BDs, as compared to controls, displayed larger amplitudes in several components of the event-related potentials (which was interpreted as greater neural activity involved in tasks performance), and these differences became to be greater after two years maintaining the BD pattern (Eduardo López-Caneda et al., 2012, 2013). Taken together, these findings are indicating that heavy alcohol consumption may lead to alterations in brain functioning in terms of increasing brain activity both during task performance (Eduardo López-Caneda et al., 2013; Wetherill et al., 2013) and also during resting state (DMN), as the present study shows.

As mentioned above, in the present study we tested both functional and structural connectivity. Regarding structural networks, we did not find any group differences neither in the pre nor in the post evaluation. Likewise, no intragroup differences in the BD group were found across time. In our view, the brain changes that occur as a result of maintaining BD alcohol consumption are measurable with electrophysiological FC techniques, but maybe the underlying structural changes are not detectable in a structural level.

Finally, the anomalous DMN FC might be considered as a marker of posterior structural and cognitive impairments linked to the maintenance of BD. In this sense, hypersynchronization has been also seen as a biomarker of brain damage in several neurological conditions such as traumatic brain injury (Castellanos et al., 2011) or in early stages of dementia (Bajo et al., 2010). In a review paper, Bryer et al (Bryer, Medaglia, Rostami, & Hillary, 2013) developed a model that explains how this brain over-activation reflects brain excitability causing network malfunctioning. In fact, in a sample of mild cognitive impairment patients, higher synchronization was a predictor factor of conversion to Alzheimer disease (Lopez et al., 2014) and also has been associated with a random network organization (Buldú et al., 2011).

In conclusion, a continued pattern of BD over at least two years appear to lead to hypersynchronized DMN as compared with the non BD group. This could be taken as a biomarker of potential brain damage caused by alcohol consumption without a clear evidence of deficits on structural connectivity. Understanding the effects of the BD pattern on FC has important implications for the etiology and prevention of future alcohol dependence. Future follow-up studies should explore weather functional networks associated with specific cognitive tasks are as well affected by BD alcohol consumption.

5.3. Experimental Study III: *Oscillatory spatial profile of Young Binge Drinkers during an equiprobable Go/NoGo task*

This study has examined the effects of binge drinking pattern on event-related theta and beta power as a function of target detection in an equiprobable Go/NoGo task. The main findings can be summarized as follows: 1) the Go and the NoGo conditions evoked different patterns of activity with greater power evoked by Go trials in both bands overall. 2) In theta band, event-related power on Go trials was lower in BD compared to the control group in the vlPFC bilaterally and the right motor area. 3) In beta band, the power on Go trials was also lower in BD group in the right vlPFC. 4) Theta band power in the vlPFC bilaterally correlates with performance accuracy and attention. Furthermore, theta power correlates negatively with the estimated BAC in the right vlPFC and with self-reported impulsivity in the left vlPFC. Overall, these results indicate that binge drinking is associated with deficient activation in theta and beta frequency bands during target detection. These effects are especially prominent in the vlPFC and in the right sensorimotor cortex, suggesting impairments in target detection and response execution. Positive correlations between vlPFC theta power and selective attention point to an important role of attentional resources that may underlie these effects. Furthermore, theta in vlPFC correlates negatively with estimated intoxication levels and with impulsivity, lending support to the idea that cognitive deficits in binge drinkers may be a consequence of increased levels of alcohol consumption that are additionally modulated by impulsivity traits.

Neurocognitive impairments in adolescent and emerging adults resulting from alcohol abuse have been well described (Zeigler et al., 2005). Particularly, several studies have revealed that BD individuals perform worse than matched controls on tasks probing prefrontal (García-Moreno et al., 2008; Goudriaan et al., 2007; Johnson et al., 2008; Nederkoorn et al., 2009a; Scaife & Duka, 2009) and attention (Hartley et al., 2004; Sanhueza et al., 2011; Townshend & Duka, 2005). Accordingly, at a psychophysiological level, abnormalities in the frontal lobe have also been found by measuring with EEG during a Go/NoGo task (Eduardo López-Caneda, Rodríguez Holguín, Corral, Doallo, & Cadaveira, 2014; Eduardo López-Caneda et al., 2012, 2013). In the present study, despite differences between groups in brain activity were found, we found similar levels between groups of behavioral performance. The most likely reason is that the scoring of the employed task has not enough accuracy to measure the subtle cognitive differences between groups, particularly in a situation where the task performance of both groups is over 90% of accuracy. However, when the psychophysiological activity measured with MEG is assessed, differences between groups exist when comparing the control population with BDs.

In order to avoid an oddball effect during the task performance, the cognitive paradigm used in the present study was an equiprobable Go/NoGo task instead of a classic Go/NoGo paradigm in which the NoGo occurs just a 20% of the cases. In this sense, a standard Go/NoGo task represents a classic paradigm in which the differing frequency of event types results in response-related processing conflict where the ACC is activated playing a key role in cognitive control by responses to low-frequency events (Braver, Barch, Gray, Molfese, & Snyder, 2001). However, since the task employed in the present study is an equiprobable Go/NoGo we did not observe any ACC activity to NoGo responses due to NoGo trials occurred with 50% probability and so did not constitute a low-frequency event.

Theta power has also been associated with engagement of executive functions in Go/NoGo tasks (Kirmizi-Alsan et al., 2006) and in response to higher working load (Jensen & Tesche, 2002). In the present study, as a result of the analysis, during the post-stimulus time window we found that the Go stimulus had greater theta power than the NoGo since the Go has greater salience for being the target to be answered. Therefore, it seems that in an equiprobale Go/NoGo task greater theta after the GO stimuli is necessary for a correct target detection and response execution. In this sense, the lower theta power in the bilateral vlPFC showed after the Go stimulus of the BD group could be reflecting impairment in target detection and response execution. In fact, given that the increased theta power in the vlPFC of both hemispheres correlated positively with the % of correct GOs in the task, it seems logical to think that BD theta power reduction could represent a decrease in the effectiveness during the task performance. Moreover, the vlPFC theta power of both hemispheres also positively correlated with the total score of the D2 attention test; and so it seems to indicate that the attentional demand that requires the task employed is also able to differentiate between BDs and controls. We can assure that theta power results are related to alcohol consumption since theta power in the right vlPFC negatively correlated with the BAC index; i.e. the higher alcohol consumption of the BD subjects, the lower theta power in the right vlPFC. Additionally, the Barratt Impulsiveness Scale correlated negatively with theta power in the left vlPFC which means subjects with lower power scored higher on self-reported impulsivity. This correlation could mean that the alcohol consumption could be modulated by impulsivity traits.

Besides, the group differences in theta power in the right motor area could be due to the effect of the handedness. The right motor area was probably reflecting voluntary movements with the left hand. Given that all the subjects were right-handedness, it seems logical to think that responding with the left hand was more challenging and therefore there was greater engagement

of the right motor cortex. This greater motor-cognitive engagement seems to be worse managed by the BD group than the control group.

As regards the relationship between alcohol and theta power, it is known that alcoholics and children with risk of developing alcoholism manifest reduced event-related theta power during cognitive task (Andrew & Fein, 2010; Porjesz et al., 2005b; Rangaswamy et al., 2007) and even during a GO/NoGo task (Pandey et al., 2016). Moreover, both event-related theta power and alcohol dependence have been linked to the same alleles in genes coding for neurotransmitter receptors (Rangaswamy & Porjesz, 2008). The present data, examining event-related oscillations in young BDs seem to extend these previous findings given that BDs, similar to alcohol-dependent patients or children with risk of developing alcoholism, displayed decreased theta activity.

Secondary, concerning beta band, it is well known that the execution of voluntary movements lead to a loss in beta power called *movement related beta decrease* (MRBD) (Pfurtscheller & Lopes da Silva, 1999). In the present results this effect is found in both motor cortices during the analyzed Go´s post-stimulus time window. On the other hand, the vlPFC cortices did not show the MRBF effect and, on the contrary, the right vlPFC showed power increased in the control group but no in the BD group. As is established, selective attention is widely considered to be righty hemisphere dominant (Corbetta, Patel, & Shulman, 2008; Shulman et al., 2010), so this power increase in the right vlPFC could be reflecting an effect of increased attention and target detection evoked by the Go stimulus that seems to be reduced in the BD group.

In summary, the present results indicate that, despite similar levels of behavioral performance, BDs manifest anomalous neural activity, as demonstrated by decreased beta and theta power in the vlPFC during response execution in an equiprobable Go/NoGo paradigm. Furthermore, the decrement in theta power correlates with worse Go accuracy response, the estimated BAC achieved in a normal binge drinking episode, worse performance in the D2 attentional test and with more impulsive personality trait (BIS). Taken together the anomalies in the vlPFC reported here may represent a neural antecedent of posterior difficulties in attention, target detection and contextual updating in BD who maintained this pattern consumption for several years; however, this possibility must be tested in extensive follow-up studies.

6. LIMITATIONS AND FUTURE DIRECTIONS

First, it is important to note that a common limitation that affects studies with this type of population is that the cross-sectional nature of this study makes it difficult to draw a conclusion about causal relationship between the neurophysiological differences and the BD consumption. It cannot be excluded that the differences between groups are previous to the consumption. In spite of this limitation, we were still able to demonstrate reliable neurophysiological differences between a BD group and control subjects in magnetic brain activity. In order to solve this limitation, our research team is carrying out a longitudinal study with 14-year-old students who will be followed-up to 18 years old. By means of this project, there will be compared the endophenotypes of young people did develop a BD patter consumption with those who did not develop this alcohol consumption.

In addition, specifically in the second study, the lack of differences between the groups in the anatomical connectivity may be due to the two years' follow-up time limitation of the study, therefore more longitudinal measures would be needed. Besides, although the sample size of the study was considerable for a follow-up study of these characteristics, a larger sample would increase the robustness of the results, and would make possible the assessing of the influence of other factors such as the sex.

Also, due to the lack of time, the result in relation to the Go/NoGo task found in the study III have not been extended with the analysis of the follow-up data. Nevertheless, the most immediate future direction will be to complete this longitudinal analysis.

Finally, the last question that remains is whether these anomalies are possible to be reversed after a long period of abstinence. This issue could be resolved with more longitudinal measures and incorporating a group of ex-binge drinkers, in the same line as other research groups have done (Eduardo López-Caneda, Rodríguez Holguín, et al., 2014; Eduardo López-Caneda et al., 2013).

In summary, the high prevalence of this behavior among young population increases the necessity of further studies in order to confirm the results and clarify the dimension of this problem.

7. CONCLUSIONS

Based on the results obtained in the tree studies and the discussion, we conclude that:

- The presence of a binge drinking alcohol consumption in young people aged 18-19 is associated with power spectral and functional connectivity differences during resting state compared with controls. The binge drinker students presented a decrease in alpha power and an increase in theta power. Regarding functional connectivity, the group of young drinkers presented a decrease of alpha band and an increase of delta, theta and beta band. Furthermore, the alpha decrease in connectivity correlated with the estimated Blood Alcohol Concentration of a representative binge episode.

- The presence of a binge drinking alcohol consumption in young people aged 18-19 is also associated with oscillatory differences during an equiprobable Go/NoGo task. Binge drinkers presented less theta and beta power in the vlPFC after the Go stimuli. This power decrement was found with similar level of performance in the task but correlated positively with the accuracy of the response and the D2 score, and negatively with the estimated BAC and with self-reported impulsivity traits. This decrement could be associated to deficits in target detection or attention of the BD group.

- The persistence in the binge drinking alcohol consumption for at least two years, from 18-19 to 20-21, is associated with an increased functional connectivity over time in the frequency bands that were already increased (delta, theta and beta). This increment in functional connectivity was found in the absence of differences between groups in structural connectivity.

- In sum, alcohol binge drinking consumption in adolescent is associated to differences in their magnetic brain activity profiles. Therefore, the high prevalence of this behavior among young population increases the necessity of further studies in order to confirm the results and clarify the dimension of this problem.

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