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DEPARTMENT OF NEUROSCIENCE, BIOMEDICINE
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Graduate school in Life and Health Sciences
PhD program in Neuroscience, Psychology and Psychiatry
cycle XXXI - 2015

Two structural neuroimaging studies in adults with Major Psychoses and Alcohol Dependence

S.S.D. MED/25

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a Claudia, Olimpia, Michela, Silvia, Giulia e Giovanna,
senza le quali Verona non sarebbe mai stata così bella

alla mia famiglia,
per aver sempre creduto in me

a Thomas,
per l'amore, il supporto e la pazienza

PREFACE

This dissertation describes the two main projects I have been working on throughout my PhD namely, (i) *The impact of Cognitive Remediation in Major Psychoses: preliminary findings* and (ii) *Sex differences in the neuroanatomical correlates of Alcohol Dependence: findings from the ENIGMA Addiction Working group,* which are the result of fruitful collaborations with scientists from different fields (e.g., psychiatrists, psychologists, engineers) I have had the pleasure to work with, in the last three years.

The first project has been carried out at the University of Verona where I actively participated in the submission and revision of the project itself as well as in the data collection (i.e., recruitment and assessment of patients with major psychosis) and analysis (i.e., behavioural and neuroimaging data).

The second project has been run at the University of Liverpool where I worked as a visiting PhD student for six months. In the UK I have approached the field of *addiction* (i.e., cannabis and alcohol use disorders) and learned specific statistical methods while working on pre-existing aggregated data (i.e., behavioural and neuroimaging). Thanks to this project I have also had the opportunity to get in touch with researchers worldwide from the ENIGMA Addiction Working Group. Background, methods, findings and main conclusions of the two projects are described below.

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ABSTRACT- project 1

The impact of Cognitive Remediation in Major Psychoses: preliminary findings

BACKGROUND: Deficits in neuro and social cognition are considered a core feature of Major Psychoses (MP) since they affect patients' functional ability and contribute to poor socio-occupational outcomes. These impairments respond mildly to antipsychotic treatments and the improvement of cognitive deficits has become a relevant target in the care of patients with MP. Specifically, clinical researchers have focused on behavioural training which utilizes a mix of cognitive exercises and generalization strategies to improve cognitive processes that support daily functioning, including Cognitive Remediation (CR).

AIMS: 1) To compare cognitive functions and brain Grey Matter (GM) volumes between patients with MP and Healthy Controls (HC). 2) To explore the effect of CR on cognition and neuroplasticity in MP. Patients undergoing CR or a Treatment As Usual (TAU) were compared for this purpose. We hypothesised that (i) MP patients relative to HC would show lower cognitive performances and reduced GM volumes; (ii) only patients treated with CR would show improvement of cognitive dysfunctions and volumetric alterations.

METHODS: Twenty patients with MP (8 females; mean age 25.45±5.29) were recruited in two research sites of northern Italy (i.e., Verona, Milan) and were matched with 20 HC (11 females; mean age 29.45±7.78). All participants underwent clinical and neuropsychological evaluations and an MRI exam at baseline (T0). Subsequently, MP patients were randomized to three groups of intervention i.e., CR + Social Skills Training (SST); CR + mindfulness and TAU and treated for three months, accordingly. After the training, clinical and neuropsychological assessments and the MRI scan were replicated in all patients. Statistical analyses were performed using SPM12, STATA 15 and SPSS 23. Due to the small sample size patients undergoing CR+SST and CR + mindfulness were merged in a single group (CR). Parametric and non-parametric tests were performed to (i) compare groups (MP patients vs HC and patients treated with CR vs TAU) on sociodemographic, clinical and cognitive variables at T0, and (ii) measure pre-post

training changes in cognitive performance associated with CR and TAU. Second, a voxel-based morphometry analysis was run to analyze MRI scans and General Linear Models were adopted to measure differences between groups in GM volumes at T0, as well as explore T0-T1 volumetric changes associated with CR and TAU.

RESULTS: Compared to HC, patients with MP showed (i) lower scores in four out of six subtests of the *Brief assessment of cognition in Schizophrenia* (BAC-S) i.e., *List Learning*, *Verbal Fluency*, *Digit Sequencing*, and *Symbol Coding*; (ii) clusters of smaller GM volumes in anterior cingulum and insula and (iii) larger GM volumes in the thalamus ($p < .05$, FWE corrected; cluster size $k \geq 200$). At baseline, no differences were found between patients undergoing CR and TAU in cognition and brain volumes. After the intervention patients undergoing CR improved marginally in the *Reading the Mind in the Eyes Test* (ESCB) and the *Digit Sequencing Test* (BAC-S) and showed trends of greater GM volumes in fronto-occipital gyri, cuneus and thalamus (all $p < .001$, uncorrected; $k \geq 100$). No pre-post training differences were observed in cognitive scores and GM volumes of patients undergoing TAU and in MP patients considered as a single group.

CONCLUSIONS: Our study suffers from some limitations that may have limited the statistical power of the analyses, most importantly the small sample size. Nonetheless, preliminary findings seem promising and suggest that CR might improve cognitive dysfunctions and determine structural neuroplasticity in patients with MP. Further analyses will be carried out to replicate the findings on a larger sample and test the long-term effect (12 months) of CR on patients' cognition and functioning. Moreover, the specific effects of CR+ SST and CR + mindfulness compared to CR alone will be also explored.

ABSTRACT – project 2

Sex differences in the neuroanatomical correlates of Alcohol Dependence: findings from the ENIGMA Addiction Working group

BACKGROUND: Male and female alcohol users show different patterns of alcohol use (e.g., age of onset, dosage) and related disorders which are likely to be influenced by neurobiological factors. However, the role of sex in the neuroanatomical correlates of alcohol dependence remains poorly examined and results are often contradictory. Discrepancies between studies may be partially due to methodological issues (i.e., small samples size and a male sampling bias) as well as to the lack of a statistically valid approach to analyse and model the effect of sex.

AIMS: 1) To measure group and group-by-sex differences in the neuroanatomy of alcohol-dependent participants (AD) and HC and explore the role of the severity of use, in a large and well-characterised sample. We focused on regions of interest (ROIs) mostly found impaired in AD including, orbitofrontal cortex (OFC), hippocampus, amygdala, nucleus accumbens, caudate, putamen, globus pallidus, thalamus, corpus callosum, cerebellum as well as global brain volumes (i.e., Grey Matter (GM), White Matter (WM), cerebrospinal fluid (CSF)). In line with previous studies, we hypothesized that all ROIs considered as well as total GM and WM may be smaller in AD versus HC and would be accompanied by CSF increases. Moreover, we expected to find group-by-sex effects in OFC, hippocampus, corpus callosum and global brain volumes.

METHODS: We pooled behavioural and MRI data from 10 research sites of the *ENIGMA Addiction Working Group*. In total, 326 HC (99 females) and 683 AD (329 females) were included in the analysis. First, ROIs were extracted using standard pipelines from Freesurfer v 5.3. Second, mixed-effect models were run to test the impact of the following variables on the ROIs (i) group, sex, and group-by-sex; (ii) monthly standard drinks (all $p \leq .05$, False Discovery Rate (FDR) corrected). All models were adjusted for major confounders including, assessment site, age, education and intracranial volume (ICV).

RESULTS: AD versus HC showed smaller GM volumes of the hippocampus, putamen, globus pallidus, thalamus, corpus callosum and cerebellum, accompanied by whole brain GM and WM shrinkage. Group-by-sex interactions were observed in the amygdala, (i.e., males AD < males HC) and cerebellar GM (i.e., females AD < females HC). Within the group of male AD, smaller amygdala volumes were predicted by greater alcohol use (all $p < .05$, FDR corrected).

CONCLUSION: In a large and well-characterised sample we confirmed that alcohol dependence is associated with neuroanatomical alterations mostly distributed in mesocorticolimbic and cerebellar circuitry which play a critical role in memory, impulse control, emotions regulation and salience attribution. These processes are commonly found altered in addiction. Furthermore, we observed, for the first time, group-by-sex interactions in the amygdala (male AD < male HC) and the cerebellum (more reduced in female AD < female HC), corroborating the hypothesis that sex plays a role in the effect of alcohol dependence on brain structures. While the exact mechanism underlying sex differences in the brain morphology of AD is unknown, both preclinical and clinical studies suggest the influence of gonadal and stress hormones that modulate alcohol's psychoactive effects via affecting brain receptors in a sex-specific manner. Longitudinal designs and comprehensive standardised assessments of alcohol dependence and relevant psychosocial outcomes will be necessary to shed some light on the mechanisms underlying sex differences in trajectories in and out of alcohol dependence related psychosocial / treatment outcomes.

Project 1

The impact of Cognitive Remediation in Major Psychoses
preliminary findings

1. BACKGROUND

Major Psychoses (MP), such as Schizophrenia and Bipolar Disorder, are heterogeneous psychiatric syndromes characterized by common clinical, cognitive and neuroanatomical features (Brambilla et al., 2011; Fischer and Carpenter Jr, 2009; Maggioni et al., 2017; Squarcina et al., 2017) that have a high prevalence in the general population (up to 1,5%) (Altamura et al., 2001) and lead to severe behavioural, relational and socio-familiar disabilities (Bonnín et al., 2010; Bora et al., 2009a; Harvey et al., 2012).

Cognitive dysfunctions, that generally persist after the acute phase of the disease, are nowadays considered a core feature of MP (Depp et al., 2012; Jabben et al., 2010; Raust et al., 2014). The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project has identified seven distinct cognitive domains that are impaired in patients with Schizophrenia including, speed of processing, attention/vigilance, working memory, verbal and visual learning, reasoning and problem solving, and social cognition (Brambilla et al., 2011; Brambilla et al., 2013; Green and Nuechterlein, 2004; Perlini et al., 2012). Similarly, patients with Bipolar Disorder perform poorly on tests of visuomotor processing speed, verbal memory, sustained attention and executive functioning although the deficits are commonly less severe and more generalized (Lewandowski et al., 2011; Mann-Wrobel et al., 2011). Notably, a growing body of evidence has shown that the presence of cognitive dysfunctions predicts worse interpersonal and socio-occupational outcomes in MP and it might be considered a marker of vulnerability for the disease (Barch and Keefe, 2009; Bryson and Bell, 2003; Burdick et al., 2010; Depp et al., 2012; Green et al., 2004; Torrent et al., 2012).

Given the more detailed knowledge of the role of cognitive deficits in MP, improvement in neuro- and social-cognition has become a primary target in the care and clinical management of the illness (Buchanan et al., 2005; Gold, 2004; Hyman and Fenton, 2003). Specifically, the focus of attention has shifted from pharmacological interventions, that proved scarce efficacy on cognition (Michael Davidson et al., 2009), to non-pharmacological interventions, such us Cognitive Remediation (CR), which focuses on the improvement of cognitive functions with

the final aim to ameliorate patients' functioning in everyday life (Wykes and Spaulding, 2011).

1.1. Cognitive Remediation in Major psychoses

1.1.1 Definition, methods and techniques

CR has been defined as *"a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalisation"* (Cognitive Remediation Experts Workshop (CREW), Florence, April 2010). CR strategies can be divided into two main categories: *compensatory* and *restorative*. *Compensatory* interventions try to remove or bypass a specific cognitive dysfunction, by means of the person's residual cognitive abilities and/or environmental resources. Indeed, the manipulation of the environment is a compensatory technique acting and operating changes in the environment in order to influence and facilitate the cognitive functions, for example, by simplifying the patient's tasks (Velligan et al., 2007). *Restorative* interventions, which are based on principles deriving from neurosciences, particularly neural plasticity, aim to correct a specific deficit trying to restore the underlying compromised function, using the ability of the brain to modify and repair itself during the whole life (Kaneko and Keshavan, 2012). Most of the CR paradigms used in psychiatry apply restorative strategies, which can be based on bottom-up or top-down approaches.

Bottom-up programs start from basic cognitive functions (i.e., simple attention, reaction time, working memory) and progress to more complex abilities (executive functions, abstract thinking, sequencing and problem solving) following a sequential (i.e., hierarchical) order (Kurtz et al., 2007; Runde Borg, 1999). Specifically, this approach utilizes 'drill and practice' methods that aim to improve attention, working memory, speed processing and abstract thinking through the repetition of exercises for specific abilities (Medalia and Choi, 2009).

By contrast, top-down protocols involve high cognitive processes from the very beginning, based on the hypothesis that basic and complex cognitive abilities can be trained in parallel and that the simultaneous engagement of multiple cognitive functions may better prepare the patients to use the skills learned in real-life

contexts. Specifically, top-down approaches are based on the implementation of new strategies (strategy coaching) and tend to favour the generalization in different contexts through the execution of different tasks that involve the use of similar strategies (Medalia and Richardson, 2005).

Overall, a variety of learning strategies are used in both compensatory and restorative interventions, although at different extents, including errorless learning, scaffolding, massed practice, and positive reinforcement and information processing strategies (Reeder and Wykes, 2006). Errorless learning avoids the implicit encoding of errors which then cannot be distinguished from correct information during the explicit recall. Similarly, the scaffolding ensures high rates of success for the learner (minimising errors) by monitoring the complexity of materials to be learned. The massed practice consists of practising with a specific task at least two-three times a week in order to favour the retention and the application of the skills acquired. Lastly, information processing strategies include, among others, breaking and simplifying the task into smaller steps, providing written prompts, self-monitoring skills, mnemonic strategies, categorization and planning (Reeder and Wykes, 2006).

CR can be administered as a standard package of exercises or customized to a single individual based on his/her specific neurocognitive profile. Some CR programs focus on single cognitive domains (e.g., working memory or facial affect recognition), while others are broad-based and focus on multiple domains at once. In recent decades, a number of CR interventions, computerized and non-computerized, designed for individual or group settings, have been developed and adopted in multimodal treatment approaches in MP. Examples of the main structured protocols are given in Table 1 (Barlati et al., 2013).

Table 1. Structured protocols of CR interventions (adapted from Barlati et al. 2013)

Cognitive Training	Target	Duration	Setting (individual/group)	Computer-assisted/ Non-computer-assisted	Restorative/ compensatory	Top-down	Bottom-up	Drill and practice	Strategy coaching	Individually tailored
IPT	Cognitive functions, social skills, and problem solving	Sessions of 60 minutes, 2-3 times a week (about 12 months)	Group (6–8)	Non-computer assisted	Restorative	+	+	+	+	−
INT	Cognitive functions and social cognition	30 biweekly sessions, 90 minutes each	Group (6–8)	Computer assisted sessions and non-computer-assisted sessions	Restorative	+	+	+	+	−
CRT	Cognitive functions	40 sessions at least 3 times a week, 45–60 minutes each one	Individual	Not computer assisted session	Restorative	+	+	+	+	+
Cogpack*	Cognitive functions	Sessions variable in duration and frequency (starting from 2-3 weeks)	Individual	Computer assisted	Restorative	−	+	+	−	+
CET	Cognitive functions and social cognition	Biweekly sessions (about 90 minutes every week) for 24 months	Group (couples and then groups of 3-4 couples)	Computer-assisted sessions and noncomputer-assisted sessions	Restorative	+	+	+	+	−

Tabella 1 *(continued)*

NEAR	Cognitive functions and problem-solving	Sessions of 60 minutes, twice a week (about 4 months)	Individual/group (3–10)	Computer-assisted sessions and noncomputer-assisted sessions	Restorative	+	−	−	+	+
NET	Cognitive functions and social cognition	Sessions of 45 minutes at least 5 times a week (about 6 months)	Individual/group	Computer-assisted sessions and noncomputer-assisted sessions	Restorative	−	+	+	−	+
CAT	Cognitive functions	Variable (short weekly visits at home, lasting about 30 minutes)	Individual	Noncomputer assisted	Compensatory	−	−	−	−	+
TAR	Social cognition	12 sessions twice a week, 45 minutes for each one	Small groups of two patients and a therapist	Computer-assisted sessions and noncomputer-assisted sessions	Restorative/ compensatory	−	+	+	+	+
SCIT	Social cognition	24 weekly sessions, 50 minutes each (about 6 months)	Group (6–8)	Computer-assisted sessions and noncomputer-assisted group sessions	Restorative	−	+	+	+	−
SCST	Social cognition	12 weekly sessions, 60 minutes each (about 3 months)	Group (6 patients)	Computer-assisted sessions and noncomputer-assisted group sessions	Restorative	−	+	+	+	−

Tabella 2 *(continued)*

SCET	Social cognition, ToM	36 sessions of 90 minutes, twice a week (about 6 months)	Group	Noncomputer assisted	Restorative	−	+	+	+	−
MCT	Metacognition	8 biweekly sessions of 45–60 minutes (one cycle per month)	Group (3–10)	Noncomputer assisted	Restorative	+	−	−	+	−
SSANIT	Cognitive functions, social cognition, and social skills	NT: biweekly sessions of 1 hour SST: weekly sessions of 2 hours Duration: 6 months	Individual (group)	NT sessions: computer-assisted SST sessions: non computer assisted	Restorative	+	+	+	+	+

CAT = cognitive adaptation training; CET = cognitive enhancement therapy; CRT = cognitive remediation therapy; INT = integrated neurocognitive therapy; IPT = integrated psychological therapy; MCT = metacognitive training; NEAR = neuropsychological educational approach to remediation; NET = neurocognitive enhancement therapy; NT = neurocognitive training; SCET= social cognition enhancement training; SCIT = social cognition and interaction training; SCST = social cognitive skills training; SSANIT = social skills and neurocognitive individualized training; SST = social skills training; TAR = training of affect recognition; ToM = theory of mind.
*Cogpack is a typical computer-assisted cognitive remediation (CACR) technique.

1.1.2. Evidence of efficacy

Various meta-analyses support the efficacy of CR in reducing cognitive dysfunctions and improving functional outcome in affective and non-affective psychoses (Bon and Franck, 2018; Grynszpan et al., 2011; McGurk et al., 2007; Revell et al., 2015; Roder et al., 2011; Wykes et al., 2011). For instance, McGurk and colleagues found that cognitive rehabilitation was associated with improvements in cognitive performance, symptoms severity and psychosocial functioning, especially in studies that provided also psychiatric rehabilitations (McGurk et al., 2007). Similarly, Wykes et al. reported partially durable effects (small-to moderate) of CR on cognition and global functioning. Interestingly, no specific treatment element (e.g., remediation approach, duration, computer, etc.) was associated with cognitive outcomes and the effect on functioning was significantly stronger when CR was administered in combination with other clinically-oriented interventions (Wykes et al., 2011). Yet, a meta-analysis by Kurtz and Richardson focusing on social cognitive interventions reported positive effects on both social cognition (i.e., facial affective recognition and ToM) and community and institutional functioning (Kurtz and Richardson, 2011). Lastly, a recent meta-analysis investigating the effect of CR in the early phase of Schizophrenia showed that (i) CR ameliorates neuro (especially verbal learning and memory) and social cognition, symptoms severity and global functioning of patients; (ii) the effect on symptoms and functioning was larger in trials with adjunctive psychiatric rehabilitation and small group interventions and (iii) the overall CR's effect sizes in early illness were smaller than those in chronic patients (Revell et al., 2015).

A meta-analysis investigating the effect of CR in schizo-affective disorders (i.e., schizoaffective disorder, affective psychosis, unipolar and/or bipolar disorders) revealed a global cognitive change after CR with effect sizes similar to those reported in the literature on patients with Schizophrenia (Anaya et al., 2012). The authors speculated that CR might have analogue benefits in affective and non-affective psychoses. Coherently, more recent studies investigating the effect of CR in Bipolar Disorder observed improvements of cognition and psychosocial functioning in patients treated with CR relative to those treated with a control therapy (Lewandowski et al., 2017; Veeh et al., 2017)

1.1.3. Neurobiological correlates

Patients with MP, particularly Schizophrenia and Bipolar Disorder, showed functional and structural neural alterations allocated in widespread brain regions, including frontotemporal cortices, paralimbic areas (i.e., anterior cingulate cortex, insula) and thalamus (Ellison-Wright and Bullmore, 2010; Maggioni et al., 2016). Accumulating evidence suggests that these regions constitute neural targets for CR, with the greater effects found in patients with Schizophrenia (Penadés et al., 2017; Ramsay and MacDonald III, 2015). Specifically, functional MRI studies demonstrated that CR normalized brain activations in several brain areas of these patients, with changes most consistently reported in prefrontal and thalamic regions (Bor et al., 2011; Edwards et al., 2010; Haut et al., 2010; Penadés et al., 2013; Wykes et al., 2002) (see Table 2 for an overview of findings, (Penadés et al., 2017)). Coherently, a meta-analysis investigating pre-post training brain activations associated with CR (i.e., Activation Likelihood Estimation approach) showed increased activity in the lateral and medial prefrontal cortex (PFC), parietal cortex, insula, and the caudate and thalamus of patients with Schizophrenia (Ramsay and MacDonald III, 2015).

Structural changes were also described in patients with Schizophrenia treated with CR, suggesting a neuroprotective effect of the intervention (Eack et al., 2010) Specifically, Eack end colleagues (Eack et al., 2010) reported that while patients in the control condition had progressive loss of Grey Matter (GM) volume in the fusiform and parahippocampal gyrus, patients receiving CR (i.e. cognitive enhancement therapy) demonstrated GM volume preservation in these areas and a significant GM volume increase in the left amygdala. These differential effects on GM changes were significantly associated with improved cognition over a two-year follow-up. However, to date, these results have not been replicated yet. Interestingly, subsequent study the same research group found that higher baseline cortical surface and GM volume broadly predicted social-cognitive response to CET (Keshavan et al., 2011).

Table 2. Overview of fMRI studies investigating changes in brain activity of patients with Schizophrenia after treatments with CR (adapted from Penades et al., 2017)

Reference	Participants	Treatment	Treatment duration (wk)	Imaging method	Experimental task	Neural treatment effects	Direction of change
Wexler et al 2000	SCZ = 8	CR	10	fMRI	Auditory verbal memory	L inferior frontal	↑
Wykes et al. 2002	SCZ = 12 HC =6	CR, CT	12	fMRI	N-back	R inferior frontal gyrus and bilateral occipital activity	↑
Rowland et al 2010	SCZ = 17 HC = 17	CR	< 1	fMRI, VBM		L amygdala, bilateral inferior parietal regions Controls also exhibited activation reductions in region and spatial extent with relational learning proficiency	↑ ↓
Edwards et al 2010	SCZ = 22 HC = 14	CR	22	fMRI	Continuous performance task	R middle frontal R superior parietal cortex R inferior frontal junction R visual cortex Cerebellum	↑↓
Bor et al 2011	SCZ = 20 HC = 15	CR	8	fMRI	N-back	L inferior/middle frontal gyrus, cingulate gyrus and inferior parietal lobule activity	↑
Subramaniam et al 2012 (PMID: 22365555)	SCZ = 31 HC = 16	AT	13	fMRI	Word generation and recognition	Medial PFC activity	↑
Penadés et al. 2013	SCZ = 31 HC = 16	CR SST	15	fMRI, DTI	N-back	L superior parietal lobule and bilateral middle frontal gyri activity DMN activity in L precuneus and middle frontal gyrus FA in CC and R posterior thalamic radiations	↑ ↓ ↑

Table 2 *(continued)*

Vianin et al. 2014	SCZ = 16	CR	8	fMRI	Verbal fluency	Inferior parietal lobule, precentral gyrus, Broca's area, middle occipital cortex, middle cingulate cortex, and superior parietal lobule activity	↑
Haut et al. 2010	SCZ = 20 HC = 10	CBSST + CR	10	fMRI	Facial affect recognition	L middle and superior occipital lobe, R inferior and superior parietal cortex, and L and R inferior frontal cortex activity	↑
Hooker et al. 2012	SCZ = 22	AT + SCT	11	fMRI	Facial emotion recognition	Postcentral gyrus activity	↑
Hooker et al. 2013	SCZ = 22	AT + SCT	11	fMRI	Facial emotion recognition	L and R amygdala, R putamen and R medial prefrontal cortex	↑

AT = Auditory-based cognitive training; CBSST = cognitive behavioural social skills training; CC = Corpus callosum; CR = Cognitive Remediation training; CT = control therapy; DMN = Default mode network; DTI = Diffusion Tensor Imaging; FA = Fractional anisotropy; fMRI = Functional magnetic resonance imaging; GM = Grey Matter; HC = Healthy Control; SCT = Social cognitive training; SCZ = Schizophrenia; VBM = Voxel-based morphometry.

1.2. What is known and what is not about Cognitive Remediation

Overall, what is nowadays known about CR is that it reduces impairments in cognition and contrast social and occupational deficits in non-affective psychoses (Lindenmayer et al., 2012; Wykes et al., 2011), especially when provided together with other rehabilitative interventions (Eack et al., 2009). Moreover, CR appears to be also a promising approach for the treatment of affective psychoses (Bowie et al., 2013; Demant et al., 2015; Lewandowski, 2016). What is not completely known is a) the potential contribution of CR when combined with a clinically-oriented intervention (e.g., social skills training; b) the degree of durability and generalization of CR effects to patients' real life; c) how CR precisely affects brain plasticity. Finally, although recent data on early psychoses suggest CR as having similar effects than those observed in chronic patients (Revell et al., 2015), to date few heterogeneous studies have tested the effectiveness of such intervention in the "critical period" of psychoses (Birchwood et al., 1998).

2. AIMS

i) To investigate differences in cognition and GM volumes between MP patients and HC, and to explore whether cognitive scores predicted volumetric alteration within the group of patients, at baseline. Based on existing evidence, we expected MP patients *versus* HC to show lower cognitive performance in speed processing, verbal and working memory, attention and executive functions, as well as GM volume reductions mostly distributed in frontotemporal cortices, anterior cingulate cortex and insula.

(ii) To explore the effect of a computer-assisted CR on patients with MP. For this purpose, we explored pre-post intervention differences in cognitive variables and GM volumes between MP patients undergoing a computer-assisted CR or usual rehabilitative interventions. We hypothesised that after the interventions (T1), patients treated with CR may show a better performance in the altered cognitive domains and greater preservation of GM volumes compared with patients undergoing TAU, possibly in limbic regions (e.g. amygdala and hippocampus).

3. MATERIALS AND METHODS

3.1 Research Framework - Cognitive remediation in patients with Major Psychoses: a multisite multimodal outcome study

This preliminary study has been conducted as part of a larger Randomized Controlled Trial (RCT) started in October 2016 i.e., *Cognitive remediation in patients with major psychoses: a multimodal multicentre outcome study* (henceforth labelled as 'RCT') which has the main objective of investigating the effect of two integrated CR interventions (i.e., CR + Social Skills Training (SST) and CR + mindfulness) versus a Treatment as Usual (TAU) in patients with MP. The considered outcomes were (i) the reduction of cognitive dysfunctions and the improvement of social, interpersonal/occupational functioning and quality of life as well as (ii) the effect on brain plasticity.

The use of real-life 'ecological batteries' will allow us to test the long-term effects of the interventions and the generalization of the results.

The RCT study is conducted by the Sections of Psychiatry of the AOUI Verona and the Ospedale Maggiore Policlinico of Milan under the supervision of Prof. Mirella Ruggeri and Prof. Paolo Brambilla, respectively. Ethical approval was obtained in both participating centres before starting the data collection. The project started in October 2016, is currently ongoing and will last approximately 3 years.

Since the design and the assessments and interventions procedures of the preliminary study and the RCT are equivalent, they have been described once, below.

3.1.1. Study design

Possibly 60 patients with a DSM-5 (Association, 2013) diagnosis of affective and non-affective psychosis will be enrolled according to specific criteria.

Inclusion criteria

- DSM-5 diagnosis of affective and non-affective psychosis
- Age range: 18-45
- Max 10 years of illness
- Stable antipsychotic therapy in the previous three months

- Stable clinical symptomatology (i.e., PANSS score 60÷80, HAM-D score < 80, Y-MRS < 11) in the previous three months

Exclusion criteria

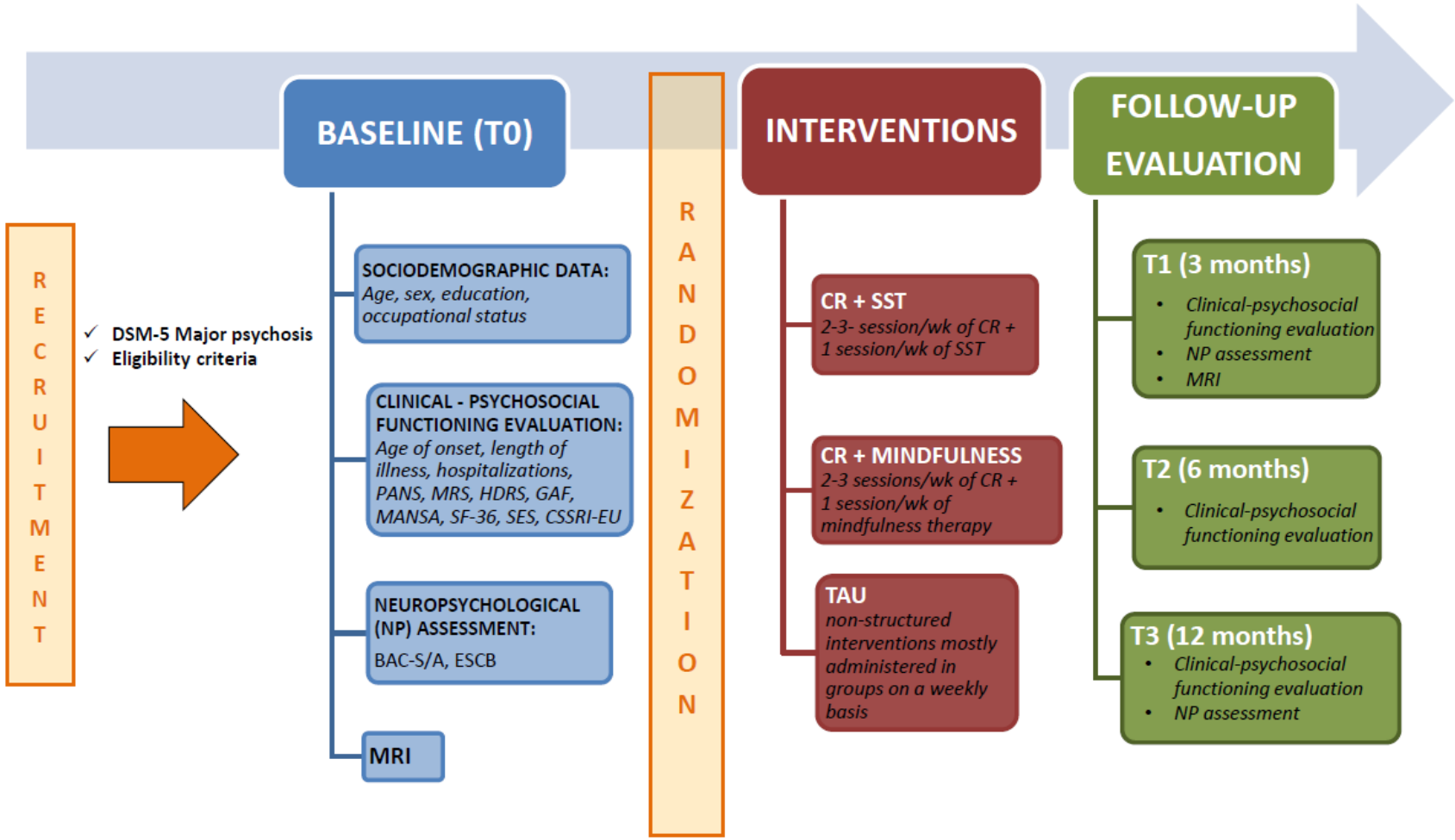
- Other psychiatric disorders or medical/neurological diseases
- Alcohol-substance abuse in the previous three months
- History of traumatic head injury with loss of consciousness
- Eyesight and/or hearing deficits
- Intellectual disability (i.e., IQ < 70)

The Structured Clinical Interview for DSM-5 Disorders: Clinician Version (SCID-5) (First and Williams, 2016) is used to confirm the diagnosis and exclude psychiatric comorbidities whereas the *Brief Intelligence Test* (Sartori et al., 1997) and *Raven's progressive matrices* (Raven, 1938) are administered to measure the IQ.

Participants enrolled in the study will undergo a baseline (T0) evaluation on sociodemographic, clinical, cognitive and social-functioning variables. Subsequently, they are randomly assigned to one of three groups of intervention (see below) and then re-assessed after 3, 6, and 12 months (T1-T2-T3, respectively). All participants undergo a 3T multimodal MRI at T0 and T1. In the post-processing analyses the following measures are obtained: volumes and thickness (with whole-brain and machine learning approaches); diffusion indices of structural connectivity (fractional and relative anisotropy mean and radial diffusivity, volume ratio, mode); resting state indices representing measures of default mode network (node degree, mean degree, hubs identification, characteristic path global, Newman modularity, global efficiency).

The flow chart of the study is illustrated in Figure 1.

Figure 1. Flow Chart of the RCT



3.1.2. Assessments and interventions procedures

Baseline assessment (T0)

Clinical and sociodemographic data including age, sex, educational level, occupational status, age of onset, length of illness, hospitalizations, and pharmacotherapy are collected and scales assessing symptoms and functioning are administered:

- *Positive and Negative Symptoms Scale (PANSS)* (Kay et al., 1987) (non-affective psychoses only)
- *Young Mania Rating Scale (YMRS) (Young et al., 1978) (affective psychoses only)*
- *Hamilton Rating Scale for Depression (HDRS)* (Reynolds and Kobak, 1995) (affective psychoses only)
- *Global Assessment of Functioning scale (GAF)* (Hall, 1995)
- *Manchester Short Assessment Quality of Life Scale (MANSA)* (Priebe et al., 1999)
- *Short Form-36 Health Survey (SF-36)* (Apolone, 1997)
- *Socio-economic Status (SES)* (Barratt, 2006)
- *Client Socio-Demographic and Service Receipt Inventory European Version (CSSRI-EU)* (Chisholm et al., 2000)

Neuro- and social-cognition are assessed through multiple instruments as described below:

- *Brief Assessment of Cognition in Schizophrenia (BAC-S) (Anselmetti et al., 2008; Keefe et al., 2004)* or *Affective Disorders (BAC-A) (Keefe et al., 2014).* The BAC-S is a brief pencil-and-paper battery for the assessment of cognition in patients with Schizophrenia which includes 6 tests: 1) List Learning Test (verbal memory); 2) Token Motor Task (motor speed); 3) Digit Sequencing Task (working memory); 4) Verbal fluency (letter and semantic fluency); 5) Symbol Coding (attention and processing speed) and 6) Tower of London Test (executive functions). The BAC-A is a battery for the assessment of 'cold' and

affective cognition in Affective Disorders that is composed by the six subtests of the BAC-S, and two additional subtests specifically designed to measure the influence of emotional salience on cognitive processes, namely the Affective Interference Test and the Emotional Inhibition Test.

- *Executive and Social Cognition Battery (ESCB) (Torralva et al., 2009).* This battery consisted of five tests including some tests of ecological validity, selected to detect alterations in social cognition and executive functions *(Caletti et al., 2013)*.

  1) Multiple Errand Test-Hospital version (MET-HV) (Knight et al., 2002): this task, commonly administered at the hospital and its surroundings, requires carrying out a number of tasks that resemble "real life" situations (e.g., collecting an envelope from a secretary, or purchasing three items), in which minor inconveniences can take place

  2) The Hotel Task (Manly et al., 2002): the test comprises six activities that would plausibly need to be completed in the course of running a hotel (e.g., making up guests' bills, sorting coins, proofreading a brochure). Patients are required to devote some time to each activity for only 15 min.

  3) The mind in the Eyes Test (Baron-Cohen et al., 2001). We adopted the Italian version of this ToM task (Serafin and Surian, 2004) where participants are presented with 17 photographs of the ocular region of different human faces and are required to choose between four options (adjectives) that best describes what the person in the presented photo is thinking or feeling.

  4) Faux Pas Test (Stone et al., 1998): Participants are asked whether something inappropriate was said in some stories that they have to read and that may contain a social faux pas. In order to understand that a faux pas has occurred, the subject has to represent two mental states: first that the person committing the faux pas is unaware that he has said something inappropriate (cognitive theory of mind) and, second, that the person hearing it might feel hurt or insulted (affective theory of mind).

  5) Iowa Gambling Task (IGT) (Bechara et al., 1994). The computerized version of the IGT mimics models real-life personal decision-making activities

in real time that include reward and punishment and the uncertainty of outcomes. Specifically, the test involves probabilistic learning via monetary rewards and punishments, where advantageous task performance requires participants to forego potential large immediate rewards for small longer-term rewards to avoid larger losses.

Interventions

After the baseline evaluation all participants are assigned to one the three groups of interventions:

1) CR + SST
2) CR + mindfulness
3) TAU

The assignment is done using single-blinded randomization with lists stratified by sex and age, to ensure a homogeneous distribution of participants between the groups.

- *CR:* the cognitive training consists of 2-3 sessions/week of computer-assisted exercises performed with Cogpack (Marker Software®) programme. Each session will be delivered individually for 45 minutes. Cogpack includes different neurocognitive exercises that can be divided into domain-specific exercises, aimed at training specific cognitive areas among those known to be impaired in Schizophrenia (verbal memory, verbal fluency, psychomotor speed and coordination, executive function, working memory, attention) (Green and Nuechterlein, 2004) and non–domain-specific exercises that require the use of various functions at the same time and engage culture, language and calculation skills (e.g., manage money). Most exercises are adaptive and the computer sets the level of difficulty, based on the patient's performance during the course of the session. The computer-assisted CR takes place preferably in the morning when the levels of vigilance and attention are higher and is preferably conducted in the same room/studio, which must not contain objects that capture the patient's attention. Patients will be guided by an operator who will help them by

providing the appropriate instructions for the activities and help for any technical problems.

- *Social Skills Training:* the SST consists of 1 group session conducted weekly by a leader and a co-leader, lasting 1,5 h. This training aims at the elimination of maladaptive behaviours via the practice of interpersonal skills in the context of specific social situations. It is based on the Social Learning Theory, which proposes that new behaviours can be acquired by observing and imitating others (Bandura, 1971). SST appears effective in improving negative symptoms and social and occupational functioning in psychosis (Turner et al., 2018). Specifically, the Bellack approach is adopted (Bellack et al., 2003). This approach suggests that complex social performance can be broken down into simpler steps and taught by therapists via modelling the correct behaviours (e.g., role-playing). Then, the skills learned in the group setting will turn to practice in the natural environment. (Bellack et al., 2003).

- *Mindfulness:* a Mindfulness-Based Cognitive Training (MBCT) (Segal et al., 2002) is conducted weekly (1,5 h) by an expert psychotherapist. This technique combines elements of meditation (e.g. body scan) and cognitive practices to help patients learning to observe sensations, and one's reactions to them, with non-judgmental awareness in order to let go the self-defeating habitual reactions to difficult experiences. We chose to combine CR with mindfulness as this intervention has been proven to be effective in reducing psychosocial distress in various physical and mental pathological conditions, including psychoses (Khoury et al., 2013). Additionally, preliminary evidence in HC showed that MBCT may improve specific cognitive processes, including working memory, meta-awareness and cognitive flexibility (Lao et al., 2016). To our knowledge, no study has so far studied the coupled effect of CR + mindfulness in psychosis.

- TAU: the '*Treatment as Usual'* will include non-structured rehabilitative interventions in a naturalistic setting of care, which are mostly administered in groups, with recreational purposes.

Follow-ups assessments (T1, T2, T3)

The evaluation of clinical symptoms and psychosocial functioning are repeated at each follow-up whereas neuro- and social-cognition are reassessed after the intervention (T1) and 12 months (T3). The MRI scan is repeated only after the intervention (T1).

3.1.3. Recruitment and Intervention status (October 2018)

To date, 20 patients (13 with non-affective psychoses; 7 with affective psychoses) were recruited in the two participating centres of Verona and Milan (Table 3) and included in this preliminary study. They carried out assessments and interventions as described in Table 4.

Table 3. Recruitment status of patients enrolled in the RCT

	Milan (N=16)	**Verona (N=4)**
Diagnosis	**Non-affective Psychosis:** 4 SCZ, 1 SFD, 1 BPD, 5 US & OPD **Affective psychosis:** 5 BD-I, 1 UB & RD	**Non-affective Psychosis:** 3 SCZ **Affective psychosis:** 1 UB & RD
Randomization	***CR + SST*** 2 SCZ, 1 BPD ***CR + mindfulness*** 1 SFD, 1 BPD, 1 US & OPD, 2 BD-I, 1 UB & RD ***TAU*** 1 SCZ, 3 US & OPD; 1 BD-I ***stand-by***[a] 1 US & OPD, 2 BD-I	***CR + SST*** 1 UB & RD ***CR + mindfulness*** 1 SCZ ***TAU*** 1 SCZ
Drop-out[b]	1 BPD (CR + SST) 1 US & OPD (TAU)	1 SCZ (CR + mind)

BPD = brief psychotic disorder; SCZ = schizophrenia; SST= social skills training SFD = schizophreniform disorder; UB & RD = Unspecified Bipolar and Related Disorder; US & OPD = Unspecified Schizophrenia Spectrum and Other Psychotic Disorder;

[a] participants who underwent T0 evaluation but have not been randomized yet

[b] participants dropped after the baseline assessment

Table 4. Assessment and intervention status

	Milan	Verona
MRI		
T0 (baseline)	13	3
T1(3 mo)	7	2
Intervention	**completed** 1 CR + SST; 4 CR + mind; 3 TAU **on-going** 1 CR + SST **stand-by** 1 CR + mind, 1 CR +SST	**completed** 1 CR + mind; 1 TAU **stand-by** 1 CR+SST
Neuropsychological assessment		
T0 (baseline)	16	4
T1 (3 mo)	8	2
T2 (6 mo)	4	
T3 (12 mo)	4	

MRI = Magnetic Resonance Imaging; mo = months

3.2. Population

Twenty patients with MP (8 females; mean age 25.45±5.29, range 19-36) were recruited at the Sections of Psychiatry of the AOUI in Verona, and Ospedale Maggiore Policlinico in Milan, as part of the RCT and they were matched with 20 Healthy Controls (HC) (11 females; mean age 29.45±7.78, range 19-42) recruited within the local community of Verona. Patients were screened and included according to the inclusion and exclusion criteria described above (section *3.1.1*). Similarly, HC were screened by expert clinicians using the Structured Clinical Interview for DSM-IV Axis Disorder Non-Patient version (First et al., 1995 314). History of psychiatric disorders, substance or alcohol use disorders, mental retardation, neurological illness or medical condition (currently under pharmacological treatment) were exclusion criteria. Standard Raven's Progressive Matrices were administered to estimate the IQ.

3.3. Assessment

All participants were briefly interviewed to collect their sociodemographic characteristics (i.e., sex, age, education and socioeconomic status). Subsequently, multiple instruments were used to assess their global functioning, clinical symptoms (patients only) and cognitive functions including, GAF, YMRS, HDRS PANSS, BAC-S/A and the ESCB (patients only). Moreover, all participants

underwent a baseline MRI scan. After the baseline evaluation (T0) patients were treated with a computer-assisted CR (either coupled with SST or mindfulness) and TAU for approximately three months. After the training, clinical and cognitive assessments, as well as the MRI scan, were replicated (T1).

3.4. Neuroimaging Data Acquisition and Processing

3.4.1. Acquisition Parameters

Imaging data were acquired using a 3-Tesla Philips Achieva MRI scanner (magnetic resonance head coil with 32 channels). All participants reclined in a supine position on the bed of the scanner and a radio frequency coil (Bruker NMR Instruments Inc., Fremont, CA) was placed over their head. Earplugs and headphones were provided to block background noise. Following a 3-plane gradient echo scan for alignment and localization, a shim procedure was performed to generate a homogeneous, constant magnetic field. A total of 165 contiguous extending superiorly from the inferior aspect of the cerebellum to encompass most of the brain were selected from a sagittal localizer scan. A high-resolution T1-weighted three-dimensional brain scan was then obtained (repetition time = 9.8 ms, echo time = 4.5 ms, field of view = 25.6 × 25.6 × 16.5 cm, flip angle = 8°, voxel size = 0.9375 mm × 0.9375 mm, slice thickness: 1 mm, slice spacing: 1 mm).

3.4.2. Neuroimaging Data Analysis

A voxel-based morphometry (VBM) analysis was performed using Statistical Parametric Mapping (SPM12) (www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in MATLAB R2017a (The Mathworks, Inc®). Before exploring the presence of GM volume differences between groups, a series of preprocessing steps have been carried out. First, all T1-weighted images were segmented according to GM, white matter and cerebrospinal fluid, bone, soft tissue, and air/background. Second, the Dartel (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) (http://www.fil.ion.ucl.ac.uk/spm/) tools were then used to determine the nonlinear deformations for registering the GM and white matter images of all participants. Finally, the resulting images were spatially normalized into the Montreal Neurological Institute (MNI) space and smoothed

with an isotropic Gaussian kernel of 6 mm full width at half maximum Gaussian kernel to increase the signal-to-noise ratio and to account for subtle variations in anatomic structures. Before the VBM analysis, we extracted the total intracranial volume (ICV) using SPM12.

3.5. Statistical analyses

Introductory notes:
1) Due to the small number of participants recruited so far, patients undergoing CR+SST and CR + mindfulness were merged in a single group (labelled as 'CR').
2) Only cognitive variables consistently measured between groups were included in the analyses as dependent variables i.e., the BAC-S scores for comparisons between MP patients and HC, and both the BAC-S and the ESCB scores for comparisons between patients undergoing CR or TAU.
3) Due to differences in scanners parameters (i.e., field strength) patients from the participating centre of Verona were excluded from MRI analyses.

All statistical analyses were performed using STATA 15 (StataCorp. 2017) and SPSS 23 (Corp, 2013). For behavioural analyses, a two-tailed significance level of $p < .05$ was adopted. For MRI analyses, inference on GM volumes differences between groups was made using double-sided t-tests ($p < .001$; cluster size $k \geq 200$ (MP vs HC) or $k \geq 100$ (CR vs TAU)). Stereotactic coordinates of the peak maxima of the suprathreshold clusters were converted from the MNI spatial array (www.mni.mcgill.ca) to that of Talairach and Tournoux. All the volumetric results were considered by proportional scaling for the participants' total ICV.

3.5.1. Cross-sectional analyses at baseline

<u>MP versus HC:</u>
First, Chi-squared tests and two sample t-tests were adopted to compare MP patients (n=20) and HC (n=20) on sociodemographic and clinical data (i.e., sex, age, education, IQ, SES, GAF, age of onset, length of disease, number of hospitalizations, pharmacological treatment (lifetime) and clinical symptoms) whereas multiple regressions, adjusted for age, sex and education, were run to

compare the two groups on cognitive measures. Second, to measure differences between MP patients (n=13) and HC (n=20) in GM volumes we performed a General Linear Model (GLM) analysis using a factorial design with 'diagnosis' as a factor of interest and nuisance covariates of sex, age and education.
Lastly, multiple regression analyses were run to investigate whether cognitive scores predicted GM volumes of MP patients (n=13, all $p < .001$, cluster size k≥ 200).

CR versus TAU:

Chi-squared tests and Mann-Whitney tests (i.e., the non-parametric equivalent of the two-sample t-test) were utilized to compare MP patients undergoing CR (n=6) and TAU (n=4) on sociodemographic, clinical and cognitive measures. Moreover, a GLM analysis was performed using a factorial design with 'intervention' as a factor of interest and nuisance covariates of sex and age ($p < .001$, cluster size k ≥ 100) to explore whether the two groups had pre-existing volumetric differences before the interventions

3.5.2. Longitudinal analyses

Longitudinal analyses were carried out to explore the potential changes occurred between T0 and T1 in MP patients, either considered as a single group or stratified by the intervention (i.e., CR vs TAU). First, we used the Wilcoxon signed-rank test (i.e., the non-parametric equivalent of the paired t-test) to explore pre-post intervention differences in cognitive measures (n=10; 6 CR, 4 TAU). Second, we employed a full-factorial GLM design with treatment and time as interacting factors to assess any specific time effects of CR (n=4) compared to TAU (n=3) on brain volumes. After GLM estimation, we inferred on 1) treatment-specific time changes, 2) treatment-by-time interactions, 3) common time changes (all $p < .001$, cluster size ≥ 100).

4. RESULTS

4.1. Sample characteristics

Compared to HC, patients with MP showed no differences in sex, age and SES, but had a lower education ($p < .001$), IQ ($p = .011$) and, as expected, lower global functioning (GAF; $p < .001$) (Table 5).

There were no differences between MP patients undergoing CR and TAU in both sociodemographic and clinical variables (i.e., sex, age, education, IQ, SES, GAF, the age of onset, length of disease, number of hospitalizations, lifetime use of mood stabilizer, antipsychotics, antidepressants and clinical symptoms) (Table 6).

4.2. Cross-sectional analyses

Compared to HC, patients with MP showed lower scores in the *List Learning*, ($p= .003$), *Verbal Fluency* ($p < .001$), *Digit Sequencing* ($p = .001$) and *Symbol Coding* ($p < .001$) tests (Table 7).

At baseline, there were no differences between MP patients treated with CR or TAU on BAC-S and ESCB scores with the exception of the *Hotel Task-time deviations* where patients undergoing TAU performed slower than those undergoing CR ($p= .049$) (Table 8).

4.2.1. Cross-sectional MRI results

Significant GM volume differences between HC and patients with MP are detailed in Table 9. Compared to HC, patients with MP showed a trend toward clusters of smaller volumes in the bilateral anterior cingulate cortex (BA24-32), insula (BA13) and cerebellum, the left middle (BA21) and superior (BA42) temporal gyri and the left inferior frontal gyrus (BA45) (all $p < .001$). Notably, clusters within the anterior cingulate cortex and insula survived a more stringent threshold of $p < .05$, peak Family Wise Error (FWE) corrected. Moreover, MP patients had (trend-level) larger volumes in the left inferior frontal gyrus (BA47), cerebellum and thalamus (left), and the bilateral putamen (all $p < .001$) relative to HC. Only the cluster within the left thalamus remained significant at $p < .05$, peak FWE corrected. The

regression analyses showed that, at baseline, cognitive scores did not predict GM volumes of patients.

There were no volumetric differences between MP undergoing CR and TAU at baseline.

4.3. Longitudinal analyses

A T0-T1 difference was observed in cognitive performances of patients treated with CR. Specifically, after the intervention (T1) patients obtained higher scores in the *Reading the mind in the eyes test* (p = .044) and, at the trend-level, in *the digit sequencing test* (p = .052) (Table 10). By contrast, neither patients undergoing TAU nor patients considered as a single group (regardless of the type of intervention) showed differences in cognitive scores between T0 and T1 (Table 11-12).

After the intervention (T1), patients undergoing CR showed trends of greater GM volumes in left superior frontal gyrus, right middle occipital gyrus, left cuneus and right thalamus (all $p < .001$, $k \geq 100$) (Table 13 and Figure 2). By contrast, no GM volumes differences were observed between T0 and T1 in MP patients undergoing TAU. Similarly, no time effects were observed in MP patients, considered as a single group (regardless of the type of intervention). Despite the presence of specific neurotrophic effects of CR, no treatment by time interactions emerged at the considered statistical threshold ($p < .001$).

Table 5. Sociodemographic and clinical characteristics of the sample (N=40)

	MP (n= 20)	**HC (n= 20)**	***Two-sample t-test*** **t**	***p***
Diagnosis (DSM-V)	6 Schizophrenia (F20.9); 1 Schizophrenia with catatonia (F20.9, F06.1); 1 Schizophreniform disorder (F20.81); 1 Brief psychotic disorder (F23); 5 Bipolar I disorder (1 manic (F31.11); 1 depressed (F31.31); 1 unspecified (F31.9); 2 with psychotic features (F31.2)); 1 Unspecified Bipolar and related disorder (F31.9); 5 Unspecified schizophrenia spectrum and other psychotic disorder (F29)			
Sex (M:F)	12:8	9:11	χ^2= 0.90	.342
Age	25.45 (5.29)	29.45 (7.78)	1.90	.065
Education	11.60 (2.87)	16.70 (2.89)	5.60	<.001***
IQ	108.53 (17.44)	120.8 (9.96)	2.68	.011*
SES	25.57 (10.69)	36.51 (16.15)	1.89	.071
GAF	59.57 (15.60)	88.00 (3.58)	7.91	<.001***
Age at onset	21.16 (5.07)			
Length of illness	4.84 (4.62)			
Hospitalizations	2.63 (2.01)			
STAB lifetime (years)	1.38 (1.78)			
AP lifetime (years)	3.91 (1.89)			
AD lifetime (years)	2.79 (1.88)			
HDRS	6.75 (4.22)			
YMRS	4.50 (4.12)			
PANSS				
positive	13.23 (6.53)			
negative	19.62 (6.87)			
psychopathology	31.54 (9.67)			
total	64.38 (18.78)			

AD = Antidepressant drug; AP = Antipsychotic drug; GAF = Global Assessment of Functioning; HC = Healthy Controls; HDRS = Hamilton Depression Rating Scale; MP = Major Psychosis patients; PANSS = Positive And Negative Syndrome Scale. SES = Socio-economic status; STAB = mood stabilizer; YMRS = Young Mania Rating Scale; yrs = years

Note: with the exception of 'sex', data are expressed as mean(sd). Differences in sex distributions are measured with the chi-square test (χ^2).

* p < .05, ** p < .01, *** p < .001

Table 6. Sociodemographic and clinical characteristics of patients with MP, stratified by the intervention (CR, TAU)

	CR (n=6)	**TAU (n=4)**	***Mann-Whitney U test*** **U**	***p***
Sex (M:F)	5:1	3:1	χ^2= 0.10	.747
Age	25 (21-34)	29 (23-34)	8.5	.453
Education[a]	12.5 (8-18)	11.5 (8-13)	11	.824
IQ	106.5 (98-127)	115.5 (98-127)	10	.668
SES	28 (16-48.33)	27.58 (18.17-37)	4	.699
GAF	55.5 (35-90)	50-60 (55)	8.5	.897
Age at onset	21 (19-34)	25.5 (13-29)	9	.517
Length of illness	3.5 (0-8)	5.5 (1-10)	9	.521
Hospitalizations	3 (1-9)	1.5 (1-4)	6.5	.228
STAB lifetime(yrs)	2 (0-5)	0 (0-2)	5.5	.225
AP lifetime (yrs)	4.5 (2-8)	4 (2-6)	11	.828
AD lifetime (yrs)	4 (2-5)	1.5 (0-5)	5.5	.258
HDRS	9 (3-10)	7.5 (7-8)	4.0	.696
YMRS	3 (2-6)	3 (2-4)	3.5	.550
PANSS				
positive	11 (10-15)	12 (8-23)	8.0	.789
negative	17.5 (13-36)	19 (18-21)	7.5	.697
psychopathology	30 (27-35)	31 (20-35)	9.0	1.00
total	60 (51-85)	62 (46-79)	8.5	.897

AD = Antidepressant drugs; AP = Antipsychotic drugs; CR = Cognitive Remediation; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; PANSS = Positive And Negative Syndrome Scale; SES = ocioeconomic status; STAB = mood stabilizer; TAU = Treatment as usual; YMRS = Young Mania Rating Scale; Yrs = years;
Note: Only participants that completed also the T1 evaluation (n=10) were included in the analysis. With the exception of 'sex', data are expressed as median(range)

Table 7. Cognitive measures of patients with MP and HC

	MP (n= 20)	**HC (n=20)**	***Multiple regressions*** **β (95% CI)**	***p***
BAC-S				
List learning test	39.10 (10.10)	50.40 (8.29)	-12.38 (-20.36, -4.39)	.003*
Digit sequencing	15.75 (3.73)	22.45 (3.35)	-5.54 (-8.74, -2.34)	.001*
Token motor task	57.60 (17.58)	66.25 (12.57)	-10.38 (-24.39, 3.63)	.142
Verbal fluency	33.75 (9.80)	54.85 (7.98)	-17.75 (-25.43, -10.06)	<.001**
Symbol coding	41.40 (10.09)	66.95 (16.01)	-28.08 (-39.40, -16.76)	<.001**
Tower of London	14.45 (3.73)	18 (3.55)	-3.05 (-6.35, 0.025)	.069

BAC-S = Brief Assessment of Cognition in Schizophrenia; CI = confidence interval; HC = Healthy Controls; MP = patients with Major psychosis; β = beta,
Data are expressed as mean(sd). Multiple regressions are adjusted for sex, age and education.
* p < .01, ** p < .001

Table 8. Cognitive measures of patients with MP undergoing CR or TAU, at T0

	CR (n=6)	**TAU (n=4)**	***Mann-Whitney U test*** **U**	***p***
BAC-S				
List learning test	44 (25-55)	34 (30-42)	6	.198
Digit sequencing	16 (12-24)	15.5 (13-19)	10	.669
Token motor task	50 (28-80)	67 (40-78)	8	.394
Verbal fluency	38 (28-52)	34 (21-42)	8	.386
Symbol coding	47 (27-52)	42.5 (41-44)	6.5	.238
Tower of London	14.5 (9-19)	16.5 (16-19)	7.5	.330
ESCB				
Met_HV				
task attempted	2 (2-3)	2 (0-3)	10.5	.693
task failures	1 (1-3)	1.5 (0-2)	11.5	.904
inefficiencies	1 (0-1)	0.5 (0-1)	8	.285
rules break	0 (0-1)	0 (0-1)	11	.789
interpretation failures	1 (0-2)	0 (0-1)	6	.165
Hotel Task				
task attempted	4 (3-5)	3.5 (1-4)	7	.264
time deviations (s)	0 (-180-276)	210 (120-360)	3	.049*
Faux Pas Test	15 (12-20)	16.5 (13-18)	10	.665
Reading the mind in the Eyes Test	19 (17-24)	28.5 (10-31)	6	.198

BAC-S = Brief Assessment of Cognition in Schizophrenia; CR = Cognitive Remediation; ESCB = Executive and Social Cognition Battery; Met_HV = Multiple Errands Test, Hospital Version; TAU = Treatment as usual. Note: Only participants that completed also the T1 evaluation were included in the analysis (n=10). Data are expressed as median(range).
* $p < .05$

Table 9: Brain regions showing significant grey matter volumes differences between patients with MP and HC

Gyrus		BA	x	y	z	cluster size	z-values	Exact p-values (cluster level)
					MP < HC			
Anterior cingulate	L	32	1	39	-8	591	4.6	< .001
	R	24	0	20	20	1443	5.6	**< .001***
Inferior Frontal	L	45	-25	-48	-34	297	4.6	< .001
Middle Temporal	L	21	-61	-25	-5	294	5.1	< .001
Superior Temporal	L	42	-61	-27	15	335	4.8	< .001
Insula	L	13	-40	6	-4	2869	5.3	**< .001***
	R	13	43	2	1	2638	5.3	**< .001***
Cerebellum	L	-	9	-59	-24	385	4.9	< .001
	R	-	-25	-48	-34	230	4.0	< .001
					HC < MP			
Inferior Frontal	L	47	-28	19	-20	227	4.7	< .001
Putamen	L	-	-31	-12	-1	598	4.7	< .001
	R		31	-10	2	532	4.7	< .001
Cerebellum	L		-28	-47	-42	440	4.1	
Thalamus	L	-	-16	20	15	746	5.4	**< .001***

BA= Brodman Area; HC = Healthy Controls; L= left; MP = patients with Major Psychosis; ; R=right.
Note: Only participants undergoing T0 MRI scans were included in the analysis (MP = 13, HC = 20).
***p < .05, peak FWE corrected**

Table 10. Cognitive measures of patients with MP treated with CR, at T0 and T1

	CR (n=6)		*Wilcoxon signed-rank test*	
	T0	**T1**	**Z**	***p***
BAC-S				
List learning test	44 (25-55)	41 (30-54)	0.94	.345
Digit sequencing	16 (12-24)	23 (12-25)	1.94	.052
Token motor task	50 (28-80)	65 (34-76)	0.95	.343
Verbal fluency	38 (28-52)	43.5 (30-56)	0.63	.528
Symbol coding	47 (27-52)	43 (25-52)	0.21	.833
Tower of London	14.5 (9-19)	16 (13-20)	1.59	.112
ESCB				
Met_HV				
task attempted	2 (2-3)	2 (2-3)	0.00	1.00
task failures	1 (1-3)	1 (0-5)	0.80	.425
inefficiencies	1 (0-1)	1 (0-1)	0.00	1.00
rules break	0 (0-1)	1 (0-2)	1.73	.083
interpretation failures	1 (0-2)	0.5 (0-1)	-1.091	.275
Hotel Task				
task attempted	4 (3-5)	4 (3-5)	0.13	.898
time deviations (s)	0 (-180-276)	0 (-180-60)	-1.19	.234
Faux Pas Test	15 (12-20)	16 (13-20)	0.33	.738
Reading the mind in the Eyes Test	19 (17-24)	23 (20-28)	2.014	.044*

BAC-S = Brief Assessment of Cognition in Schizophrenia; CR = Cognitive Remediation; ESCB = Executive and Social Cognition Battery; Met_HV = Multiple Errands Test, Hospital Version.
Data are expressed as median (range). Note: Only participants that completed also the T1 evaluation were included in the analysis (n=6).
* $p < .05$

Table 11. Cognitive measures of patients with MP undergoing TAU, at T0 and T1

	TAU (n=4)		*Wilcoxon signed-rank test*	
	T0	**T1**	**Z**	***p***
BAC-S				
List learning test	34 (30-42)	36 (32-43)	0.92	.375
Digit sequencing	15.5 (13-19)	16 (13-18)	0.00	1.00
Token motor task	67 (40-78)	68 (62-74)	1.63	.103
Verbal fluency	34 (21-42)	31 (26-31)	-0.54	.593
Symbol coding	42.5 (41-44)	46 (30-50)	0.00	1.00
Tower of London	16.5 (16-19)	18 (14-18)	-0.82	.414
ESCB				
Met_HV				
task attempted	2 (0-3)	3 (1-3)	1.73	.083
task failures	1.5 (0-2)	0 (0-2)	-1.40	.161
inefficiencies	0.5 (0-1)	1 (0-2)	1.00	.317
rules break	0 (0-1)	0.5 (0-3)	1.40	.162
interpretation failures	0 (0-1)	0 (0-0)	-1.00	.317
Hotel Task				
task attempted	3.5 (1-4)	4.5 (3-5)	1.73	.083
time deviations (s)	210 (120-360)	-30 (-64-142)	-1.46	.144
Faux Pas Test	16.5 (13-18)	17 (12-18)	-0.186	.853
Reading the mind in the Eyes Test	28.5 (10-31)	23.5 (14-27)	-0.92	.357

BAC-S = Brief Assessment of Cognition in Schizophrenia; ESCB = Executive and Social Cognition Battery; Met_HV = Multiple Errands Test, Hospital Version; TAU = Treatment as usual; Data are expressed as median(range). Note: Only participants that completed also the T1 evaluation were included in the analysis (n=4).

Table 12. Cognitive measures of patients with MP at T0 and T1, regardless of the intervention delivered

	MP (n=10)		*Wilcoxon signed-rank test*	
	T0	**T1**	**Z**	***p***
BAC-S				
List learning test	39.5 (25-55)	40 (30-54)	-0.41	.683
Digit sequencing	16 (12-24)	22 (12-25)	-1.74	.083
Token motor task	61 (28-80)	68 (34-76)	-1.49	.138
Verbal fluency	36 (21-52)	31 (26-56)	-0.24	.813
Symbol coding	43.5 (27-52)	43 (25-52)	0.12	.906
Tower of London	16 (9-19)	16 (13-20)	-1.14	.254
ESCB				
Met_HV				
task attempted	2 (0-3)	2 (1-3)	-1.34	.180
task failures	1 (0-3)	1 (0-5)	-0.17	.869
inefficiencies	1 (0-1)	1 (0-2)	-0.64	.523
rules break	0 (0-1)	1 (0-3)	-2.22	.270
interpretation failures	0.5 (0-2)	0 (0-1)	-1.39	.166
Hotel Task				
task attempted	4 (1-5)	4 (3-5)	-1.49	.136
time deviations (s)	120 (-180-360)	0 (-180-142)	-1.90	.057
Faux Pas Test	15 (12-20)	16 (12-20)	0.11	.917
Reading the mind in the Eyes Test	21 (10-31)	23.5 (14-28)	-1.03	.301

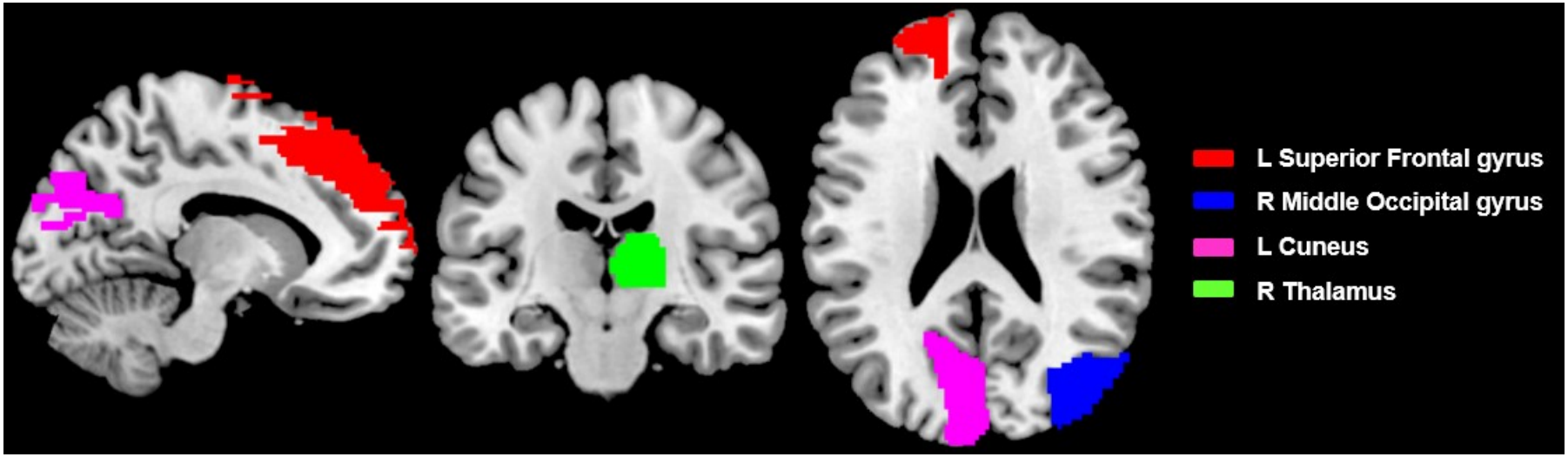
BAC-S = Brief Assessment of Cognition in Schizophrenia; ESCB = Executive and Social Cognition Battery; Met_HV = Multiple Errands Test, Hospital Version; TAU = Treatment as usual, Data are expressed as median(range). Note: Only participants that completed also the T1 evaluation were included in the analysis (n=10).

Table 13. Grey matter volumes differences between T0 and T1 in patients treated with CR

Gyrus		BA	x	y	z	cluster size	z-values	Exact p-values[a] (cluster level)
					T1>T0			
Superior frontal	L	11	-21	40	18	121	5.3	<.001
	R	11	9	59	-21	144	4.1	<.001
Middle occipital	R	18	10	-95	16	210	4	<.001
Cuneus	L	18	-10	-97	10	444	4.8	<.001
Thalamus	R	-	7	-23	-1	831	4.3	<.001

BA= Brodman Area; L=left; R=right. Note: Only participants that underwent MRI scan at T1 were included in the analysis (CR=4). [a] all $p < .001$, uncorrected

Figure 2. Brain regions showing increased grey matter volumes in patients with MP undergoing CR, after the intervention



all $p < .001$ uncorrected; cluster size $k \geq 100$

5. DISCUSSION

5.1. Comparisons between patients with MP and HC

The first objective of our study was to compare cognitive functions and GM volumes between patients with MP and HC. We hypothesised that MP patients would show lower cognitive scores in processing speed, verbal and working memory, attention and executive functions, and reduced GM volumes relative to HC mostly distributed in frontotemporal cortices, anterior cingulate cortex and insula. Our results confirmed these hypotheses.

Patients with MP performed worse than HC in 4 out of 6 subtests of the BAC-S namely, *List learning, Semantic and Letter Fluency, Digit Sequencing* and *Symbol Coding* which measure verbal memory and fluency, working memory and attention and processing speed, respectively. Our findings are consistent with previous evidence concerning the neuropsychological profile of patients with MP (either affective and non-affective) (Bora et al., 2009b, 2010; Bowie et al., 2018; Harvey and Rosenthal, 2018; Kurtz and Gerraty, 2009; Robinson et al., 2006). Specifically, there is a large body of data showing that patients with Schizophrenia exhibit cognitive alterations in several cognitive domains, including speed of processing, attention/vigilance, working memory, verbal and visual learning, reasoning and problem solving, and social cognition (Brambilla et al., 2011; Brambilla et al., 2013; Green and Nuechterlein, 2004; Perlini et al., 2012). Coherently other studies suggest that, despite being less severe, cognitive deficits in Bipolar Disorder qualitatively overlap with those in Schizophrenia (Harvey et al., 2010; Lewandowski et al., 2011; Mann-Wrobel et al., 2011).

The volumetric comparison between MP patients and HC revealed that patients had significant GM volume reductions mostly distributed in the anterior cingulate and the insula and, to a less significant extent, in frontotemporal gyri and the cerebellum. These findings concur with previous structural MRI studies on neuroanatomical correlates of MP (Hallahan et al., 2011; Nortje et al., 2013; Shepherd, Alana M. et al., 2012). Specifically, a number of VBM meta-analyses reported GM volume deficits in insula, cingulate cortex, medial frontal gyri and middle and superior temporal gyri in patients with Schizophrenia (Ellison-Wright

and Bullmore, 2010; Robyn Honea et al., 2005) as well as in anterior cingulate cortex, inferior frontal gyrus, insula, middle and superior temporal gyri and pole in patients with Bipolar Disorder (Ellison-Wright and Bullmore, 2010; Selvaraj et al., 2012), relative to HC, ultimately suggesting a common neuroanatomical substrate among these conditions. Other studies comparing Schizophrenia and Bipolar Disorder patients further corroborate this hypothesis (Calvo et al., 2019; Maggioni et al., 2017; Squarcina et al., 2017). For instance, a VMB meta-analysis by Yu et al. (2010) showed substantial overlaps between brain volumes affected by Schizophrenia and Bipolar Disorder including the prefrontal cortex, thalamus, left caudate, left medial temporal lobe and right insula (Yu et al., 2010). Consistently, a recent review on voxel-based comparisons between patients with these diseases demonstrated overlapping GM reduction in the insula and anterior cingulate (Maggioni et al., 2016). Lastly, a recent European metacentric study by our group revealed common volumetric reductions in patients with Schizophrenia and Bipolar Disorder compared to HC in three clusters located in the superior temporal, anterior / midcingulate and occipital cortices (Maggioni et al., 2017). Lesions incorporating the insula may reduce the capacity of integrating external stimuli and thus weaken motivated or appropriate emotional responses (Gasquoine, 2014). Resulting impairments are evident, for example, in decision making and social cognition (Gasquoine, 2014) which are both hallmarks of Schizophrenia (Shepherd, Alana M et al., 2012; Wylie and Tregellas, 2010). Moreover, a growing body of works suggests that insular and anterior cingulate cortices may be considered together as input and output regions of a functional system namely, the *salience network* (Palaniyappan and Liddle, 2012). Structural and functional alterations of this network are common in MP and lead to a variety of cognitive-affective dysfunction, such as emotional awareness, interoception and information processing deficits (Palaniyappan and Liddle, 2012; White et al., 2010).

5.2.Pre-post training comparisons between patients undergoing CR and TAU

The second objective of our study was to investigate the effect of a computer-assisted CR on cognitive performances and GM volumes of patients with MP. For this purpose, we compared MP patients undergoing CR and TAU before and after

the interventions. In line with our hypotheses, trends of cognitive improvement and neuroplasticity were observed in patients treated with CR only. Specifically, after the training, these patients obtained trend-level higher scores at the *Digit Sequencing Task* of the BAC-S and significantly higher scores at *The Reading the Mind in the Eyes Test* of the ECSB. Similarly, they showed a trend toward larger GM volumes in fronto-occipital regions and in the thalamus. Worth noticing, no differences in clinical and cognitive variables as well as brain volumes were revealed between patients treated with CR and TAU at baseline suggesting that our results should have not been influenced by pre-existing differences in cognitive functioning and brain atrophy between the two groups. Overall, our preliminary findings are consistent with existing research demonstrating that CR, specifically in a computer-assisted form, improves a wide range of cognitive domains and social cognition in patients with affective and non-affective psychoses (Anaya et al., 2012; Bowie et al., 2018; Grynszpan et al., 2011; Lindenmayer et al., 2008; McGurk et al., 2007; Vita et al., 2011; Wykes et al., 2011). For instance, Poletti and colleagues found that patients with Schizophrenia treated with computer-assisted CR versus those undergoing a placebo training, had significant long-term improvements for executive function, attention and psychomotor coordination (Poletti et al., 2010). Similarly, Deckersbach et al. reported that a 14-session CR program designed to treat both residual symptoms and cognitive impairment in people with Bipolar Disorder was effective in reducing depression and improving executive functions and psychosocial functioning (Deckersbach et al., 2010).

Our experiment also suggested that CR may determine structural neuroplasticity. This results is particularly interesting in view of the fact that, to date, only one study revealed neurostructural changes associated with CR, including long-term GM volumes preservation (i.e., fusiform and parahippocampal gyrus) and increase (i.e., amygdala) in patients with Schizophrenia undergoing CR relative to HC (Eack et al., 2010). Furthermore, our preliminary findings are coherent with previous literature showing functional plasticity in patients with Schizophrenia treated with CR relative to HC (Ramsay and MacDonald III, 2015). Functional MRI studies comparing pre-post training brain activations showed that CR leads to increased activity in widespread brain regions, which may indicate strengthened cortical

engagement resulting from training (Ramsay and MacDonald III, 2015). Particularly, increased activations were most consistently reported in prefrontal (i.e., superior, middle and inferior), parietal and occipital (i.e., middle and superior) cortices, as well as in the insula, caudate and thalamus (Bor et al., 2011; Edwards et al., 2010; Haut et al., 2010; Hooker et al., 2012; Penadés et al., 2013; Rowland et al., 2010; Subramaniam et al., 2012; Subramaniam et al., 2014; Vianin et al., 2014; Wykes et al., 2002). Of note, activation associated with CR in the left PFC and thalamus/cuneus partially overlapped with previous meta-analytically identified areas associated with deficits in working memory, executive control, and facial emotion processing in Schizophrenia (Delvecchio et al., 2013; Glahn et al., 2005; Minzenberg et al., 2009).

5.3 Limitations

Our study suffers from some limitations, which should be taken into account when interpreting the results. First, the small sample size might have limited the statistical power of the analyses. For instance, non-parametric tests and uncorrected p-values have been used for comparisons between patients undergoing TAU and CR. Moreover, the sample was no large enough to explore the specific effect of CR coupled with SST or mindfulness as all patients undergoing CR were merged in a single group (regardless of the additional intervention delivered) and whether CR outcomes were influenced by the diagnosis (i.e., affective vs non-affective psychosis). Second, the RCT did not include a group treated with CR only in the first place, thus we could not distinguish the effect of CR alone from these of CR coupled with SST or mindfulness. Noteworthy, a study granted by the Ministry of Health (GR-2016-02361283, principal investigator Dr. Cinzia Perlini) has been recently approved and will be carried out in our lab, comparing cognitive measures and structural and functional indices of patients with non-affective psychoses (i.e., Schizophrenia Spectrum and Other Psychotic Disorders) undergoing CR alone, CR+SST and CR+mindfulness. Third, since the information about recent pharmacotherapy was not available, the influence of antipsychotics and mood stabilizers on brain volumes findings cannot be excluded, although patients were in the first ages of their conditions. Lastly, a further limitation may have arisen from

differences observed in education and IQ scores between patients with MP and HC. However, education was included as a covariate in all comparisons between the two groups (IQ was not included as it was significantly correlated with education, $r = 0.42$, $p < .009$).

5.4. Conclusions

Overall, our preliminary findings on the effect of CR in patients with MP are promising and show an emerging effect of the training on both cognitive functioning and structural neuroplasticity. Further analyses on a larger sample size will be carried out in our lab in order to investigate the long-term effectiveness of CR on cognitive, clinical and psychosocial functioning as well as to clarify whether CR determines structural and functional neuroplasticity. Similarly, analyses stratified by type of intervention (i.e., CR, CR+SST, CR+mindfulness) and diagnosis will be run to explore the distinct effects of CR alone and combined with other behavioural therapies.

Project 2

Sex differences
in the neuroanatomical correlates of Alcohol Dependence
findings from the ENIGMA Addiction Working group

The Sections that follow have been extracted and adapted from

"Rossetti MG, Patalay P; Mackey S, Batalla A, Bellani M, Chye Y, Conrod P, Cousijn J, Garavan H, Solowij, Suo C, Thompson PM, Yucel M., Brambilla P, Lorenzetti V & the ENIGMA Addiction Working Group. Males and Females with alcohol dependence show distinct neuroanatomical alterations: Findings from the ENIGMA Addiction Working Group (2018)" (manuscript in preparation).

1. BACKGROUND

1.1. Sex differences in patterns of alcohol use and related disorders

Alcohol use disorders (AUD) have devastating consequences on physical and mental health and represent 5% of the total global burden of disease, ultimately resulting in three million deaths annually (Erol and Karpyak, 2015; Organization and Unit, 2014).

Substantial sex differences have been reported in alcohol use and its consequences. For instance, females start drinking at later ages and consume lower quantities of alcohol but they progress more rapidly from first use to dependence (i.e., telescoping effect) and, those who drink excessively, have higher risks of medical and psychiatric comorbidities (Flensborg-Madsen et al., 2011; Mann et al., 2005; Mann et al., 2004). Conversely, males drink more frequently and are more likely to develop AUD (Brennan et al., 2011; Chung et al., 2012; Organization and Unit, 2014). Yet, males with AUD enter treatment programs later and tend to achieve worse long-term outcomes than females (Alvanzo et al., 2014; Bravo et al., 2013; Lewis and Nixon, 2014). These differences are likely to be influenced by neurobiological factors (Erol and Karpyak, 2015; Nixon et al., 2014) thus, to better understand what may cause sex dimorphism in drinking patterns and alcohol dependence consequences it is essential to disentangle whether alcohol affects the brain of males and females differently, as well as, the neural mechanisms mediating alcohol-related addictive behaviours in both sexes.

1.2. Neuroanatomical alterations associated with Alcohol Dependence

Animals models show that alcohol dependence is underpinned by neurobiological changes in selective cortical-striatal-limbic regions associated with different stages of the addiction cycle (i.e., binge/intoxication, withdrawal/negative affect,

preoccupation/anticipation) in which impulsive and compulsive behaviours dominate at the early and last stages, respectively. These regions include the ventral tegmental area, dorsal striatum, nucleus accumbens, thalamus, globus pallidus, extended amygdala, hippocampus, insula and prefrontal cortices (Koob and Volkow, 2010). Consistently, neuroimaging studies in humans found that alcohol dependence is associated with neuronal loss in widespread brain regions including, prefrontal cortices (i.e., dorsolateral, orbitofrontal), the hippocampus, amygdala, striatum, thalamus, corpus callosum and cerebellum, which are often accompanied by global reductions in GM and white matter (WM) and cerebrospinal fluid (CSF) increases (Dupuy and Chanraud, 2016; Sawyer et al., 2016; Zahr, 2014; Zahr and Pfefferbaum, 2017).

1.2.1. The role of sex

The role of sex differences in the neurobiology of alcohol dependence remains poorly examined and results are sparse (Nixon et al., 2014; Sawyer et al., 2017). Males and females with alcohol dependence showed smaller and larger dorsolateral PFC respectively, in comparison with their non-dependent counterparts (Sawyer et al., 2017). By contrast, adolescent females with AUD displayed smaller PFC volumes than female controls, while the opposite pattern was found in males (Medina et al., 2008). Both alcohol-dependent males and females had smaller right hippocampus and larger CSF than controls of the same sex, whereas only among females left hippocampus was also smaller (Agartz et al., 1999). Dependent versus non-dependent females also showed reduced corpus callosum, an effect not found in males (Hommer et al., 1996) but, in a more recent study, both sexes reported volume deficits in this region with a stronger group difference among dependent males (Ruiz et al., 2013). Yet, both males and females with alcohol dependence had reduced total GM and WM and larger CSF compared to controls, with a greater effect among females (Hommer et al., 2001). By contrast, significant shrinkage of total GM and WM volumes and ventricular enlargement was shown in dependent versus non-dependent males, but not among their female counterparts (Pfefferbaum et al., 2001). Lastly, higher severity of drinking (e.g., monthly dosage, lifetime use) has been associated with reduced volumes in distinct areas in dependent females

(e.g., frontal, temporal, ventricles) and males (e.g., corpus callosum and cerebellum) (Ruiz et al., 2013; Sawyer et al., 2016). Of note, other works failed to find sex differences in alcohol-dependent versus control groups in several brain regions, including cingulate and insular cortices, amygdala, hippocampus, nucleus accumbens, cerebellum as well as GM, WM and CSF volumes (Demirakca et al., 2011; Mann et al., 2005; Mechtcheriakov et al., 2006; Pfefferbaum and Sullivan, 2002; Sawyer et al., 2017). To sum, only a paucity of studies to date have investigated sex differences in the neuroanatomical correlates of alcohol dependence, showing mixed effects. Discrepancies between studies may stem from methodological issues including, small samples sizes and a male sampling bias; heterogeneity with regard alcoholic population and alcohol use characteristics; inconsistent control for major confounders (i.e., age, education), other substance of use (i.e., tobacco) and psychiatric comorbidities; the measurement of global instead of regional volumes (Sawyer et al., 2017) and lack of a statistically valid approach to evaluate the influence of sex (Durazzo et al., 2014; Gilbertson et al., 2008; Lind et al., 2017) (Sawyer et al., 2017). Interestingly, a recent meta-analysis that investigated sex disparities in structural neuroimaging research on substance use disorders, observed an underrepresentation of females compared to males for all drug classes but alcohol was the most male biased, with nearly 30 % of studies including no females in their sample population (i.e., 24 out of 87 between 1992 and 2015). Yet, three-quarters of the studies (regardless of the substance of use) did not evaluate or report sex effects and used a statistical approach that precluded detection of group-by-sex interactions (e.g. within-sex analyses) (Lind et al., 2017).

2. AIMS AND HYPOTHESES

The present study aimed to investigate sex differences in the neuroanatomical correlates of alcohol dependence, above and beyond the effect of major confounders (i.e., intracranial volume (ICV), age and education), using a multilevel statistical approach that accounts for dependency between observations in nested designs. We measured group differences and group-by-sex interactions in a large and well-characterised cohort comprising 326 healthy controls (HC) and 683 alcohol-dependent individuals (AD) recruited from the ENIGMA addiction working group, focusing on a *priori* regions of interest (ROIs) strongly associated with alcohol dependence including, the lateral and medial orbitofrontal cortex (OFC), hippocampus, amygdala, striatum (nucleus accumbens, caudate, putamen), globus pallidus, thalamus, corpus callosum, cerebellum (GM and WM) as well as total GM, WM and CSF. Within alcohol-dependent males and females, we also explored the relationship between severity of recent drinking (i.e., monthly dosage) and brain volumes. We hypothesized that (i) AD relative to HC would show volume deficits in all a *priori* ROIs accompanied by total GM and WM shrinkage and CSF increase; (ii) group-by-sex interaction effects may be found in the OFC, hippocampus, corpus callosum and in global brain volumes and (iii) female AD would be more sensitive to the effect of higher dosage of alcohol than male AD.

3. MATERIALS AND METHODS

The present study has been pre-registered in May 2017 on *Open Science Framework*), an open source website that facilitates collaboration and transparency in scientific research.

3.1. Population

Participants' neuroimaging and clinical data were gathered from 10 research sites in the ENIGMA Addiction Working Group, including the University of New Mexico, Albuquerque (site 1, n=442; site 2, n=186); Yale University, New Haven (site 3, n=129); National Institutes of Health Clinical Center, Bethesda (site 4, n=351); University of Amsterdam, Amsterdam (site 5, n=62; site 6, n=52; site 7, n=40); University of Barcelona, Barcelona (site 8, n=29); University of Wollongong, Wollongong (site 9, n=18) and Monash University, Melbourne (site 10, n=38).

Research sites obtained approval from local ethics committees and study participants provided written informed consent at their local institution.

The original sample consisted of 1348 subject. Of these, we carefully screened and excluded 161 AD with lifetime/current psychiatric comorbidities and/or current substance dependence (other than alcohol) to exclude the effect of these disorders on brain volumes (Brady and Sinha, 2005; Grodin and Momenan, 2017; Uhlmann et al., 2018), 15 AD with abstinence > 30 days, as prolonged abstinence has been associated with neuroadaptations and may confound our findings (Gazdzinski et al., 2005; Sullivan et al., 2005; van Eijk et al., 2013) and 15 AD with IQ < 80. Similarly, we excluded participants with missing values for any variable of interest namely, sex (68 AD) and education (31 AD, 41 HC) as well as participants with MRI artefacts (1 HC). Additional inclusion and exclusion criteria that were applied at each of the sites are detailed in Table 14.

In total, we analyzed data from 1009 participants, comprising 326 HC (99 females, 31%) and 683 AD (329 females, 48%) without psychiatric comorbidities, current substances dependence other than alcohol (AD only), cognitive disabilities and general MRI contraindications.

Participants' demographic characteristics and substance use levels (i.e., alcohol, tobacco) were assessed through semi-structured interviews at each individual site (Table 14). These included age, sex, education, monthly standard drinks and monthly cigarettes.

Table 14. Assessment instruments by imaging site

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10
Inclusion criteria, alcohol dependence										
Alcohol group	√	√	√	√	√	√	-	-	-	-
Control group	√	√	√	√	√	√	√	√	√	√
Inclusion criteria, alcohol dependence										
DSM-IV	√	Drinking occasion ≥ 5 (men) ≥ 4 (women) ≥ 5 in past/mo	√	√	√	AUD	-	-	-	-
Exclusion criteria, all participants										
SCID-I	√	√	√	√	MINI plus	CIDI	MINI	PRISM	√	√
IQ < 80	-	-	-	√		√	-	-	-	-
Age < 18 years	-	-	-	-	-	√	-	-	-	-
Female	-	-	-	-	-	-	-	√		
MR contraindication	√	√	√	√	√	√	√	√	√	√
Use of psychoactive medication	√	√	√	√	√	√	√	√	√	√
Severe alcohol withdrawal	√	√								
Left-handed								√	√	
Current drug abuse or dependence*	√	√	√		√	√	√	√	√	
Positive toxicology (urine, blood, breath) test results										
Alcohol, illicit drugs							√	√	√	√
Urine screen, (MR day)	√	√	√	√	√	√				
Alcohol breath test (MR day)	√	√	√	√	√					

Table 14 *(continued)*

Measures of alcohol / tobacco use										
AUDIT	√	√	-	-	√	√	-	-	-	-
TLFB	√	-	-	√	-	-	-	-	-	-
StDr/mo	√	√	√	√	√	√	√	√	√	√
Cig/mo	√	√	√	√	√	√	-	√	√	√
MRI scanner parameters										
3T	√	√	√	√	√	√	√	√	√	√
voxel size 1mm^3 iso	√	√	√	0.9x0.9x1-1.5mm^3	√	√	1x1x1.2mm^3	√	√	√
MPREAGE	√	√	√	√	-	-	-	-	-	√
echo	5-echo multi-echo	5-echo multi-echo	n.d.	n.d.	Gradient Echo	Gradient Echo	Turbo Field Echo	Spoiled Gradient Recalled Echo	Spoiled Gradient Recalled Echo	n.d
matrix	256x256x176	256x256x176	256x256x176	256x256x176	256x231x170	256x256x170	256x256x182	56x256x180	256x256x180	256x256x176
flip angle	7°	7°	7°	6°	8°	8°	8°	8°	8°	12°
TR	2530ms	2530ms	2530ms	4.57.8ms	9ms	9ms	9.6ms	6.4ms	6.4ms	1900ms
TE	1.64, 3.5, 5.36, 7.22 & 9.08ms	1.64, 3.5, 5.36, 7.22 & 9.08ms	3.34ms	2.2-3.1ms	3.6ms	4.20ms	4.6ms	2.9ms	2.9ms	2.15ms

*other than alcohol abuse or dependence in the alcohol-dependent group; AUD = Alcohol use disorder; AUDIT = Alcohol Use Disorders Identification Test (Saunders et al., 1993); Cig = cigarettes; MINI = Mini Neuropsychiatry International Interview (Lecrubier et al., 1997); mo = month; International Diagnostic interview (Robins et al., 1988); n.d. = not described; occ = occasion; PRISM = Psychiatric Research Interview for Substance and Mental Disorders (http://www.columbia. edu/~dsh2/prism/, Hasin et al. 1996); SCID = Structured Clinical Interview for DSM Disorders (First et al., 1994); StDr= standard drinks; TLFB = Time-line Follow back (Sobell and Sobell, 1992); TE= Echo time; TR = Repetition time.

3.2. Neuroimaging data acquisition and processing

Structural T1-weighted MRI scans were prepared locally using FreeSurfer 5.3 (http://sufrer.nmr.mgh.harvard.edu/), a fully automated MRI processing pipeline that identifies 7 bilateral subcortical and 34 bilateral cortical ROIs (Dale et al., 1999; Desikan et al., 2006). Then, quality control procedures were performed following standardized and publicly available imaging protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/) specifically designed to reduce variability across sites. Lastly, the volume of a *priori* ROIs, including the OFC (lateral, medial), hippocampus, amygdala, nucleus accumbens, caudate, putamen, globus pallidus, thalamus, corpus callosum, cerebellum (GM, WM) as well as total brain volumes (GM, WM and CSF) were extracted and served as dependent variables for further analyses.

3.3. Statistical analyses

Statistical analyses were performed using STATA 14 (StataCorp; 2015). First, two-way ANOVAs and chi-square tests compared groups on demographic characteristics (sex, age, education), monthly standard drinks and cigarettes, and ICV. Second, we performed a series of mixed-effect models to test our hypotheses. This method statistically accommodates dependence between observations in nested designs (i.e., participants within sites). *Site* was treated as a random effect to account for the systematic site-level variation in the dependent variables expected to occur from differences in scanners, protocols and assessments and the extent of variation explained by these site-level differences was estimated as an intra-class correlation (ICC). All models were adjusted for major confounders including age, education and ICV.

Model 1 was run to investigate the impact of group and group-by-sex in ROI volumes of alcohol-dependent versus control groups. Then, Cohen's *d* was used to estimate the size of significant effects. It is worth noting that to check if the effects may be influenced by tobacco use (Durazzo and Meyerhoff, 2007; Durazzo et al., 2014), we selected a subsample with tobacco use data (140 controls, 488 AD) and replicate Model 1 twice, with and without tobacco among the confounders. We

observed that, when tobacco was included, results did not change and hence have increased confidence that findings are not due to confounding with tobacco use.

Model 2 was run within males and females AD to explore the association between brain volumes and alcohol use levels. The distribution of 'monthly standard drinks' values were positively skewed (skewness = 2.03), therefore, we applied a square root transformation to this variable (skewness = 1.00) before running Model 2.

A False Discovery Rate (FDR) corrected statistical threshold of p(FDR) < .05 was applied to control for multiple comparisons (Benjamini and Yekutieli, 2001; Newson, 2010).

4. RESULTS

4.1. Sample characteristics

Participants' demographic and substance use characteristics and ICV, are shown in Table 15. AD and HC were matched by sex, however, AD were significantly older, had lower education and larger ICV and, as expected, they had higher levels of alcohol and tobacco use.

4.2. MRI findings

Table 16 overviews volumetric measures by group and sex and Figure 3 summarizes significant group-by-sex effects. AD relative to HC had significantly smaller volumes in the hippocampus (d = -0.13), left putamen (d = -0.07), left globus pallidus (d = -0.05), right thalamus (d = -0.11), corpus callosum (d = -0.14), cerebellar GM (d = -0.07) as well as total GM (d = -0.09) and total WM (d = -0.11) Cerebellar GM reductions were more marked in females (than males) with alcohol dependence versus their control counterpart (d = -0.19 and d = -0.06, respectively). In males but not in females, amygdala volumes were smaller in alcohol-dependent versus HC (d = -0.10). Smaller amygdala volumes were predicted by higher alcohol dosage in alcohol-dependent males only (Figure 4) (all $p < .05$, FDR corrected).

Table 15. Sample characteristics

	HC		*AD*		*Group (AD vs HC)*			Group-by-Sex	
	Males	*Females*	*Males*	*Females*	df	F	p	F	p
Sex[a], N	227	99	444	239	-	-	-	-	-
Age	30.44 (10.57)	29.76 (10.15)	34.59 (10.41)	33.00 (10.50)	(1-1008)	23.92	<.001**	0.37	.543
Education	15.14 (2.95)	15.63 (2.86)	14.01 (2.36)	14.27 (2.53)	(1-1008)	43.69	<.001**	0.37	.545
StDr/mo	28.66 (30.15)	17.51 (22.05)	188.36 (179.40)	109.95 (107.07)	(1-717)	113.50	<.001**	8.08	.005*
Cig/mo	25.07 (91.27)	42.85 (101.39)	175.58 (234.27)	144.26 (230.87)	(1-627)	32.80	<.001**	1.25	.265
ICV (10^6)	1.44 (0.25)	1.24 (0.23)	1.62 (0.21)	1.42 (0.17)	(1-1008)	129.47	<.001**	0.04	.841

AD= Alcohol Dependent, Cig/mo= monthly cigarettes; ICV= intracranial volume; StDr/mo = monthly standard drinks, Values for age, education, alcohol use, tobacco use and ICV are mean (sd).
[a] Differences in sex distribution measured with chi2 test: $\chi 2 = 2.12$, $p = 0.146$
* $p < .01$, ** $p < .001$

Table 16. Overview of brain volumes in alcohol-dependent individuals and healthy controls

		HC		AD						
Volumes		*Males*	*Females*	*Males*	*Females*	*Group (AD vs Controls)*		*Group-by-Sex*		Site[§]
(mean(sd))		*(n = 227)*	*(n= 100)*	*(n=444)*	*(n =239)*	β (95% CI)	*p*	β (95% CI)	*p*	Var
medial OFC	L	5246,85 (751,08)	4701,97 (680,31)	5107,32 (652,07)	4593,40 (645,39)	25,91 (-142,71; 194,53)	.763	-125,57 (-286,77; 35,63)	.127	23
	R	5322,67 (743,46)	5006,09 (644,98)	5066,19 (644,69)	4667,74 (619,73)	-150,07 (-317,23; 17,10)	.079	-3,30 (-156,99; 163,59)	.968	19
lateral OFC	L	7982,47 (992,69)	7303,38 (862,22)	7486,76 (883,49)	7013,06 (850,35)	-121,20 (-331,51; 89,11)	.259	-268,55 (-469,29;-67,83)	.009	.26
	R	7640,83 (1074,53)	6998,46 (886,78)	6968,81 (855,4)	6492,55 (813,50)	-151,90 (-375,56; 71,79)	.183	-177,40 (-390,76; 35,97)	.103	.27
Hippocampus	L	4349,54 (517,54)	4053,65 (450,20)	4157,60 (512,99)	3973,67 (447,50)	-195,90 (-322,54; -69,25)	**.002***	-91,98 (-213,43; 29,48)	.138	.24
	R	4453,53 (544,65)	4162,94 (446,34)	4278,54 (499,13)	4035,58 (422,63)	-211,87 (-338,09; -85,64)	**.001***	-44,19 (-165,47; 78,00)	.475	.21
Amygdala	L	1737,01 (272,17)	1547,13 (261,50)	1595,20 (221,63)	1487,09 (187,38)	-15,07 (-77,14; 47,00)	.634	-85,04 (144,24; -25,83)	.005	.36
	R	1833,44 (296,25)	1600,01 (230,75)	1607,55 (216,91)	1486,64 (209,31)	6,43 (-5,54; 69,42)	.841	-112,00 (-172,02; -51,98)	**<.001***	.40
Nucleus accumbens	L	690,10 (200,32)	647,63 (169,96)	529,56 (128,20)	478,71 (125,03)	-14,16 (-47,25; 18,93)	.402	-34,04 (-65,47; -2,61)	.034	.63
	R	684,93 (161,57)	625,76 (147,35)	608,64 (127,11)	566,22 (117,90)	-23,17 (-54,04; 7,69)	.141	-35,06 (-64,40; -5,72)	.019	.56
Caudate	L	3929,38 (478,33)	3631,15 (443,44)	3815,56 (507,07)	3495,81 (464,24)	-13,00 (-137,54; 111,54)	.838	-27,27 (-146,65; 92,12)	.654	.25
	R	4094,54 (542,91)	3735,19 (501,98)	3886,63 (523,18)	3530,29 (511,15)	-22,58 (-156,02; 110,85)	.740	-45,79 (-172,93; 81,36)	.480	.41
Putamen	L	6315,64 (933,10)	5851,62 (86467)	5724,20 (791,36)	5236,20 (681,31)	-362,52 (-565,85; -159,19)	**.001***	-18,09 (211,79; 175,61)	.855	.42
	R	6037,24 (874,82)	5527,51 (779,47)	5480,04 (732,23)	4996,81 (678,87)	-192,41 (-377,54; -7,27)	.042	-67,79 (-244,09; 10,51)	.451	.44

Table 16 *(continued)*

Globus pallidus	L	1683,30 (290,45)	1537,25 (30476)	1705,86 (295,68)	1496,13 (265,01)	-107,69 (179,17; -36,21)	**.003***	74,97 (6,83; 143,10)	.031	.39
	R	1682,90 (228,64)	1557,33 (210,71)	1543,00 (218,57)	1376,37 (191,14)	-59,66 (-117,60; -1,71)	.044	-14,59 (-69,88; 40,71)	.605	.35
Thalamus	L	8324,35 (1059,85)	7688,46 (950,51)	8289,65 (881,16)	7707,98 (878,87)	-124,27 (-338,71; 90,17)	.256	-233,45 (-437,73; -29,17)	.025	.42
	R	7704,08 (749,21)	7085,12 (623,99)	7688,46 (829,46)	7029,74 (778,56)	-342,49 (-528,49, -156,49)	**<.001***	-18,59 (-196,39; 159,21)	.838	.30
CC		337726 (59873)	3214,01 (478,03)	324964 (55067)	317209 (53695)	-250,62 (-402,28; -98,96)	**.001***	-58,33 (-203,75; 87,08)	.432	.19
Cerebellar *GM*	L	49748,97 (12223,38)	45350,75 (10674,25)	49776,49 (10079,69)	46901,45 (5353,79)	-4912,23 (-6618,42; -3206,15)	**<.001***	2.680,16 (1.064,12; 4.296,20)	**.001***	.53
	R	50681,09 (12255,99)	46880,50 (10597,60)	51398,51 (10217,81)	48296,37 (5567,04)	-4975,89 (-6711,65; -3240,13)	**<.001***	3.114,74 (1.470,75; 4.758,73)	**.001***	.53
Cerebellar *WM*	L	14762,27 (3327,16)	14037,49 (3261,05)	15480,42 (3199,86)	15511,41 (3267,66)	-535,75 (-1310,19; 238,69)	.175	217,95 (-517,98; 953,90)	.562	.37
	R	14917,15 (3477,19)	14031,98 (3071,54)	15777,06 (3379,94)	15833,47 (2900,10)	-671,71 (-1428,16; 84,74)	.082	160,89 (-557,47; 879,24)	.661	.39
Total GM		645538,63 (69823,91)	587412,59 (63758,74)	627424,44 (65675,21)	579092,83 (58721,07)	-14246,61 (-23872,33; -4620,89)	**.004***	-10.484,85 (-19.624,72; -1.344,99)	.025	.40
Total WM		509147,64 (53259,68)	445501,06 (44096,16)	489119,80 (57098,48)	436710,17 (48121,77)	-21329,92 (-32618,17;-1004166)	**<.001***	-13.117,49 (-23800,79; 2.434,19)	.016	.59
CSF		984,87 (278,31)	947,42 (243,35)	1132,24 (238,95)	995,04 (213,05)	63,10 (-2,39; 128,60)	.059	25,48 (-37,53; 88,48)	.428	.16

AD= Alcohol Dependent participants; CC = Corpus Callosum; CI = confidence interval; CSF= cerebrospinal fluid; GM = Grey Matter; HC= Healthy Controls; L=left; OFC = orbitofrontal cortex; R=right; ROI = Region of Interest, β = beta, Var = variation, WM = White Matter

[§]Site-level variation estimated as an intraclass correlation (ICC).

*** p <.05, FDR corrected**

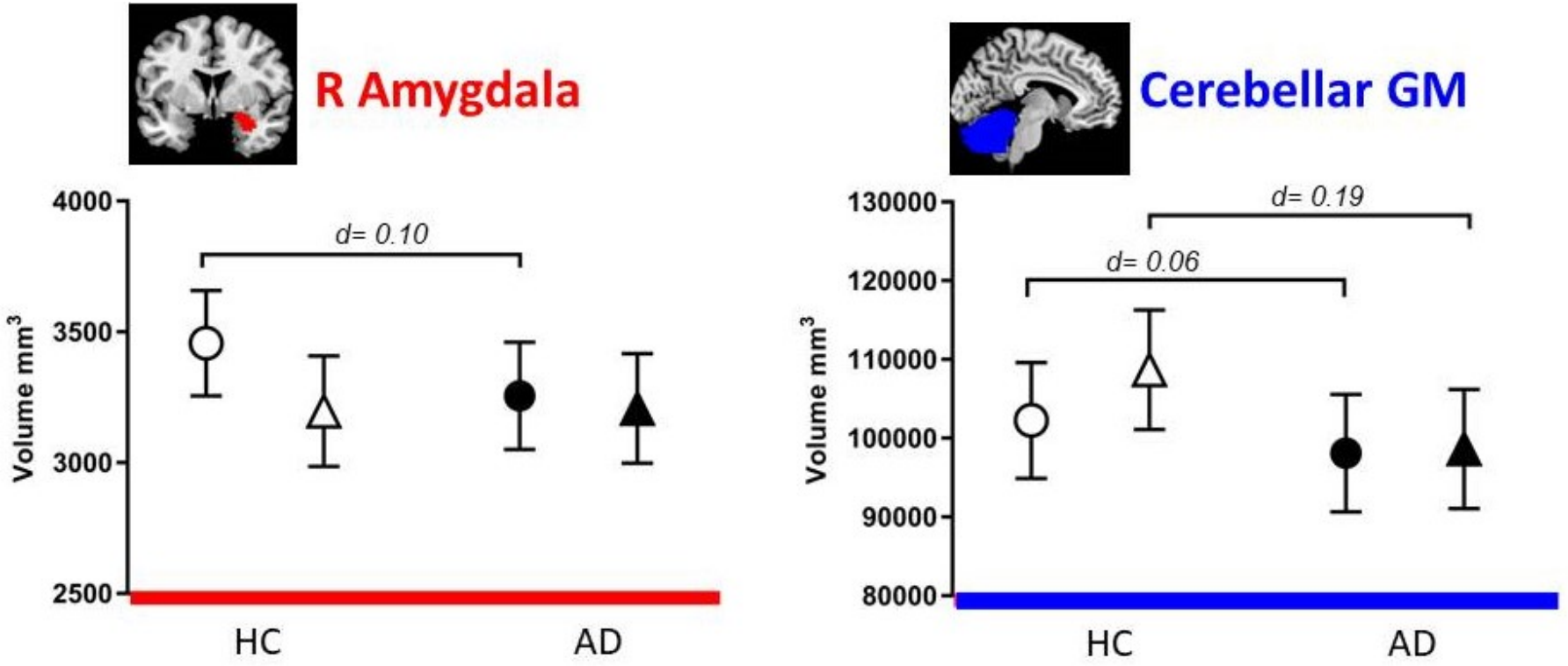
Table 17. Associations between brain volumes and monthly standard drinks in males and females with alcohol dependence

Volumes		AD males (n = 321)		AD females (n = 186)	
		β (95% CI)	*p*	β (95% CI)	*p*
medial OFC	L	-4.14 (-16.73, 8.45)	.519	4.05 (-18.18, 26.27)	.721
	R	-13.25 (-25.19, -1.30)	.030	-15.54 (-36.51, 5.44)	.147
lateral OFC	L	-9.85 (-25.42, 5.72)	.215	-19.32 (-46.77, 8.121)	.168
	R	-6.56 (-23.03, 9.90)	.435	-1645 (-44.09, 11.20)	.244
Hippocampus	L	-10.23 (-20.57, 0.12)	.053	-13.99 (-29.01, 1.04)	.068
	R	-11.22 (-20.80 -1.65)	.022	-19.45 (-33.91, -4.99)	.008
Amygdala	L	-8.05 (-12.95, -3.15)	**.001***	-8.55 (-15.87, -1.23)	.022
	R	-7.71 (-12.42, -3.00)	**.001***	-7.82 (-15.58, -0.05)	.048
Nucleus	L	-2.75 (-5.36, -0.14)	.039	-2.61 (-6.86, 1.65)	.230
accumbens	R	-1.39 (-3.98, 1.19)	.291	-5.49 (-9.49, -1.49)	.007
Caudate	L	-10.02 (-20.13, 0.09)	.052	-2.51 (-17.28, 12.25)	.739
	R	-10.72 (-20.94, -0.50)	.040	-4.50 (-20.85, 11.86)	.590
Putamen	L	-13.54 (-30.83, 3.75)	.125	-17.58 (-40.15, 4.99)	.127
	R	-6.95 (-22.50, 8.61)	.381	-12.94 (-35.11, 9.24)	.253
Globus	L	-8.74 (-14.35, -3.12)	.002	-2.47 (-11.01, 6.08)	.571
Pallidus	R	-1.23 (-6.05, 3.58)	.615	-2.39 (-9.81,5.03)	.528
Thalamus	L	-4.45 (-20.32, 11.42)	.583	-8.60 (-38.06, 20.86)	.567
	R	-11.42 (-26.53, 3.70)	.139	-13.41 (-37.53, 10.71)	.276
Corpus Callosum		-12.61 (-24.38, -0.84)	.036	-3.16 (-23.76, 17.44)	.764
Cerebellar	L	58.99 (-63.31, 181.29)	.334	-4.27(-162.80, 154.27)	.958
GM	R	56.33 (-65.26, 177.91)	.364	12.48 (-148.71, 173.68)	.879
Cerebellar	L	-2.03 (-54.27, 50.21)	.939	-18.31 (-109.12, 72.50)	.693
WM	R	21.44 (-35.09, 77.96)	.457	-38.10 (-138.11, 61.92)	.455
Total GM		-842.71 (-1539.67 -145.74)	.018	-1640.93 (-3010.37, -271.48)	.019
Total WM		-1175.91 (-2055.37, -296.45)	.009	-376.81 (-1969.96, 1216.33)	.643
CSF		6.19 (1.11, 11.27)	.017	5.12 (-2.27, 12.51)	.175

AD = Alcohol Dependent participants; CSF = cerebrospinal fluid; GM = Grey Matter; L= left; mid = middle; OFC = orbitofrontal cortex; R=right; ROI = Region of Interest, β = beta, WM = White Matter. Note: only AD with monthly standard drinks data were included in the analysis (n=507)

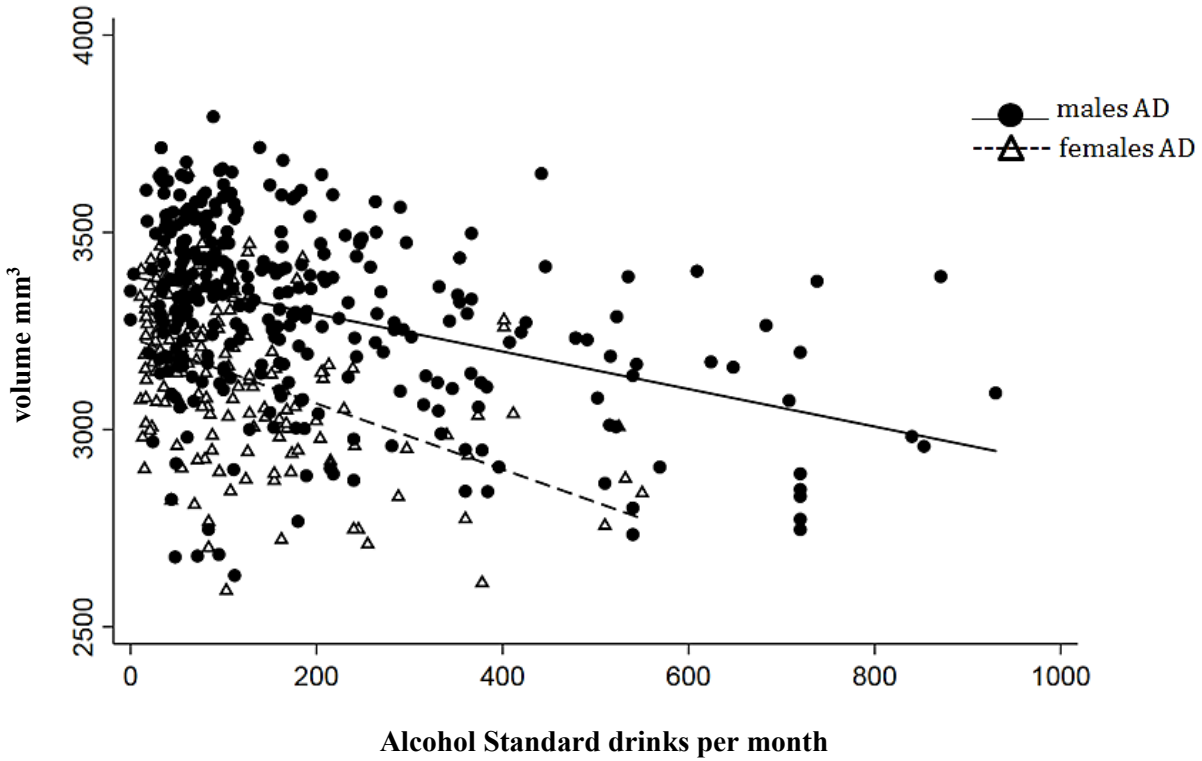
*** p <.05, FDR corrected**

Figure 3. Significant group-by-sex effects at p < .05, FDR corrected



Vertical and horizontal bars represent 95% confidence interval and significant group-by-sex effects, respectively. m = males, f = females

Figure 4. Amygdala volume by alcohol use in male and female alcohol-dependent participants



Note: The volumes of the amygdala were collapsed across hemispheres. Only the association in the male group remained significant after FDR correction.

5. DISCUSSION

Using a large and well-characterised sample, we aimed to investigate the effect of group and group-by-sex on the neuroanatomical correlates of Alcohol Dependence, controlling for the influence of major confounders including ICV, age and education. We were a priori interested in the OFC, hippocampus, amygdala, striatum, globus pallidus, corpus callosum, cerebellum and global GM, WM and CSF, areas previously found altered in AD and/or with a key role in the neuropathology of addiction (Koob and Volkow, 2010; Zahr, 2014).

In line with previous evidence, AD relative to HC showed smaller hippocampus, putamen, globus pallidus, thalamus, corpus callosum and cerebellar GM accompanied by total GM and WM shrinkage (Agartz et al., 1999; Beresford et al., 2006; Cardenas et al., 2007; Chanraud et al., 2007; De Bellis et al., 2005; Demirakca et al., 2011; Hommer et al., 2001; Mechtcheriakov et al., 2006; Ruiz et al., 2013; Sawyer et al., 2016; Sullivan et al., 2005; Wilhelm et al., 2008). As expected, AD had no larger volumes compared to HC, however partially in contrast with previous evidence, no group differences were observed in the OFC, amygdala, nucleus accumbes and caudate (Boutte et al., 2012; Cardenas et al., 2011; Durazzo et al., 2011; Fein et al., 2006; Makris et al., 2008; Sullivan et al., 2005). This may be attributable to samples and methodological discrepancies that may limit the comparability of the findings including, the smaller and mostly male-biased samples, the heterogeneous AD groups (e.g. AD with early or protracted abstinence, outpatients/inpatients) and the lack of systematic controls for major confounders (i.e., ICV, age, education) or multiple comparisons in previous studies (Boutte et al., 2012; Cardenas et al., 2011; Durazzo et al., 2011; Fein et al., 2006; Makris et al., 2008; Sullivan et al., 2005).

Overall, we broadly replicated prior evidence of smaller regional and global volumes in AD, confirming that alcohol dependence is associated with neuroadaptations predominantly in mesocorticolimbic and cerebellar circuitry which play a critical role in memory, impulse control, emotions regulation and salience attribution processes which are altered in addiction (Koob and Volkow, 2010; Moulton et al., 2014).

Widespread global volumetric reductions in our alcohol-dependent group resemble those observed in ageing, suggesting that alcohol may exacerbate ageing (Guggenmos et al., 2017), although we did not have a longitudinal sample to test this hypothesis. The conduct of future longitudinal studies comparing alcohol-dependent and control group is warranted.

The primary aim of our study was to identify sex differences in association with alcohol dependence and brain morphology. We observed significant group-by-sex reductions in the right amygdala (i.e., males AD < males HC), and cerebellar GM (i.e., more marked in females AD < females HC). In contrast with our hypothesis, there was no effect of group-by-sex in the hippocampus and the corpus callosum. Nonetheless, the few studies that previously showed interactions in these ROIs had smaller samples size (i.e. ≤ 98 participants) (Agartz et al., 1999; Hommer et al., 1996; Ruiz et al., 2013), used a different statistical methods (i.e. within-sex analysis) (Agartz et al., 1999; Ruiz et al., 2013) and did not control for ICV, age, education simultaneously (Agartz et al., 1999; Hommer et al., 1996; Ruiz et al., 2013) compared with our study, ultimately suggesting that discrepancies between results may be related to differences in methodological approaches.

To the best of our knowledge, this is the first time a relationship between sex differences and alcohol dependence is shown in amygdalar and cerebellar volumes. We observed that males AD had smaller amygdala than males HC an effect not found in females. Partially in line with this result, a recent study investigating sex differences in the brain reward system of AD found that alcohol-dependent males had smaller total reward network volumes (i.e., aggregated cortico-limbic volumes, including the amygdala) than non-alcoholic males (Sawyer et al., 2017). The amygdala is part of a common neuroanatomical substrate (i.e., the extended amygdala) that integrates stress responses and reward processing to produce the unpleasant emotional states characteristic of alcohol (or other substances) withdrawal which ultimately support the negative reinforcement processes associated with the development of addiction (Koob and Volkow, 2010). Humans studies suggested that males versus females with alcohol dependence tend to display greater and more severe alcohol withdrawal symptoms (Deshmukh et al., 2003; Soyka et al., 2006; Wojnar et al., 1997). Similarly, preclinical studies

revealed that males rats or mice experience greater alcohol-related withdrawal symptoms than females, either physical (i.e. seizure susceptibility) and motivational (i.e., anxiety-like responses) (Alele and Devaud, 2007; Reilly et al., 2009; Tanchuck-Nipper et al., 2015). For instance, a recent work testing sex-dependent alterations in an animal model of alcohol withdrawal-induced anxiety found that males versus females rats had enhanced negative affect behaviours and reduced signalling and expression of certain brain receptors in the amygdala (Henricks et al., 2017). Thus, amygdala volumetric reduction in males with alcohol dependence may reflect greater sensitivity to alcohol-induced withdrawal symptoms (e.g., anxiety) in human and animal alcohol-dependent males versus females (Alele and Devaud, 2007; Deshmukh et al., 2003; Reilly et al., 2009; Soyka et al., 2006; Tanchuck-Nipper et al., 2015) although this does not fully explain putative mechanism underlying amygdala reductions associated with alcohol dependence. Notably, smaller amygdala volumes were associated with higher monthly standard drinks suggesting that the amygdala in males is more susceptible to the neurotoxic effect of chronic high level of alcohol exposure. Alternatively, sex differences in amygdala volumes of AD may be due to premorbid volumetric differences between males and females who start drinking (Squeglia et al., 2012) and, in turn, indicate that neuroanatomical discrepancies in certain regions may represent a sex-specific risk factor for the development of alcohol dependence.

There was also a group-by-sex interaction cerebellar GM, showing greater volume deficits in females versus males AD compared with their same-sex HC. This result in is line with a large (although mixed) body of works suggesting that females are more sensitive to deleterious effects of alcohol misuse than males, including accelerated progression to dependence (i.e., telescoping) (Agartz et al., 1999; Mann et al., 2005; Piazza et al., 1989) and greater brain atrophy (Agartz et al., 1999; Hommer et al., 1996; Hommer et al., 2001). Yet, an enhanced susceptibility to the neurotoxic effects of ethanol in females versus males has also been reported in preclinical studies (Alfonso-Loeches et al., 2013; Becker and Koob, 2016; Butler et al., 2009; Tanchuck-Nipper et al., 2015) although not unanimously (Becker and Koob, 2016; Tanchuck-Nipper et al., 2015). Of note, in our study, no volume-dosage association was observed in the cerebellar GM of either males or females

AD suggesting that variables other alcohol-related and unrelated variables may account for group and group-by-sex effects within this region, such as age of onset of alcohol use, cumulative lifetime dosage, psychiatric symptoms, stressful life events. While the exact mechanism underlying sex differences in the brain morphology of AD is unknown, both preclinical and clinical studies suggest the influence of gonadal and stress hormones that modulate alcohol's psychoactive effects via affecting brain receptors in a sex-specific manner, especially in the reward circuitry (Carroll and Anker, 2010; Evans and Levin, 2011; Kiesner, 2012; Strong et al., 2009; Witt, 2007).

5.1. Limitations

It is important to stress that our results should be viewed in light of some potential limitations. We had limited measures of alcohol exposure, which precluded the examination of the role of other alcohol-related variables on volumetric reductions e.g., age of alcohol use /dependence onset, cumulative lifetime dosage, binge episodes, alcohol dependence symptom scores (Ruiz et al., 2013; Sawyer et al., 2016). Another limitation is that, while we excluded comorbid substance use and mental health disorders, psychopathology symptoms and personality scores associated with alcohol dependence (e.g., depression, anxiety, impulsivity) were not measured and could not be examined in relation to volumetric measures. The limited alcohol and mental health data was due to their inconsistent assessments across studies (i.e., measured via heterogeneous instruments or not assessed in some studies) and warrants the development of a minimum set of standardised tools to assess alcohol dependence, related psychosocial outcomes and comorbid drug use, so that future (including multi-site) studies - can measure the specificity and the functional significance of the findings. Third, our findings may have been influenced by noise due to inter-site heterogeneous MRI methodology (e.g., MR strength, manufacturer, acquisition parameters), behavioural assessment protocols, samples demographic and mental health characteristics. These were mitigated using standardized MR quality check protocols (Thompson et al., 2014; van Erp et al., 2016) and multilevel statistical approach (Lind et al., 2017), the latter of which accounted for age and education. Yet, this was the largest structural neuroimaging

study to date to examine sex differences in a sample of participants with current alcohol dependence confirmed with standardised clinical tools i.e., DSM-IV, screened for comorbid psychopathologies and substance dependence. Finally, the cross-sectional study design precluded the understanding of whether neuroanatomical differences predated/followed the onset of alcohol dependence and exacerbated with its course.

5.2. Conclusion

Our findings validate and advance existing knowledge on the role of alcohol dependence, sex differences, and alcohol dosage on neuroanatomy using a large scale multi-site structural neuroimaging study, in a carefully selected sample screened for major psychiatric comorbidities and using a robust statistical design. Alcohol dependence was associated with widespread volumetric reductions encompassing medial temporal (hippocampus), striatal (putamen, pallidum, thalamus), corpus callosum, global brain volumes (total grey and white matter). Sex differences in the neuroanatomy of alcohol dependence emerged in the volumes of specific brain regions. These include the volumes of cerebellum grey matter, which was reduced more prominently in females, and of the amygdala, which showed a dose-dependent reduction only in dependent males.

These findings have implications to advance neuroscientific theories of addiction that implicate the amygdala and cerebellum in drug withdrawal and addiction but do not account for sex differences. Our results highlight the need to account for sex differences in neuroscientific studies of alcohol dependence using multimodal imaging studies that map distinct properties of neural integrity (e.g., brain anatomy, function and neurotransmitters), longitudinal designs and comprehensive standardised assessments of alcohol dependence and relevant psychosocial outcomes. This work will be necessary to shed some light on the mechanisms underlying sex differences in trajectories in and out of alcohol dependence related psychosocial / treatment outcomes and to match the treatment demands posed by increasing rates of substance use disorders in women (Greenfield et al., 2010).

ACKNOWLEDGEMENTS

Completing this dissertation would have not been possible without the support of wonderful people around me. First of all, I would like to thank my supervisors Prof Paolo Brambilla and Dr Marcella Bellani. Thank you both for encouraging me to work independently and for having always been present despite the distance between us. Secondly, I want to thank Dr Valentina Lorenzetti and Dr Praveetha Patalay who have been driving my project at Liverpool University. Thank you both for the warm welcome and for the team working; your feedbacks gave me countless opportunities to become a better scientist. My gratitude goes also to Giuseppe and Eleonora who helped me with the statistical analyses and to Niccolò for proofreading the manuscript. Last but not least, I would like to thank some colleagues I have had the pleasure to work with during these three years, including Veronica, Cinzia, Filippo, Alessandra, Letizia and Gianluca.

EPILOGUE

I would like to leave the reader with two essential lessons I learned during my PhD, which I believe influenced me the most during my 'journey' as a young researcher

1. Science needs time

Behind a scientific project, there is a hard work of scientists who spend days studying what the scientific community is missing, in order to come up with interesting research questions and put their ideas into practice. Quite often, those scientists have to deal with long bureaucratic procedures, participants' recruitment difficulties, unforeseen events and countless errors that make them fail and start over. During the PhD, I had the opportunity to work on some projects from the very beginning and this helped me to become aware that rigorous science is time-consuming. Please see the inspiring '*Slow Science Manifesto'* below.

2. Teamwork leads to the best achievements

Teamwork is a must. It gives researchers the opportunity to benefit from each other's expertise and strengths collaborations among them. Moreover, it improves science' accuracy. No good researcher works alone.

The SLOW SCIENCE MANIFESTO

"We are scientists. We don't blog. We don't twitter.
We take our time. Don't get us wrong—we do say yes to the accelerated science of the early 21st century. We say yes to the constant flow of peer-review journal publications and their impact; we say yes to science blogs and media & PR necessities; we say yes to increasing specialization and diversification in all disciplines. We also say yes to research feeding back into health care and future prosperity. All of us are in this game, too.
However, we maintain that this cannot be all. Science needs time to think. Science needs time to read, and time to fail. Science does not always know what it might be at right now. Science develops unsteadi-ly, with jerky moves and un-predict-able leaps forward—at the same time, however, it creeps about on a very slow time scale, for which there must be room and to which justice must be done.
Slow science was pretty much the only science conceivable for hundreds of years; today, we argue, it deserves revival and needs protection. Society should give scientists the time they need, but more importantly, scientists must take their time.
We do need time to think. We do need time to digest. We do need time to mis-understand each other, especially when fostering lost dialogue between humanities and natural sciences. We cannot continuously tell you what our science means; what it will be good for; because we simply don't know yet. Science needs time.

—Bear with us, while we think."

Source: http://slow-science.org/

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