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PSYCHOSES, LANGUAGE AND BRAIN ASYMMETRY: fMRI CONNECTIVITY ALTERATIONS IN BIPOLAR DISORDERS.

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Ἐν ἀρχῇ ἦν ὁ λόγος
In principio erat verbum
In the beginning was the Word

John of Patmos

In girum imus noctē
et consumimur igni
We wander by night
and we are burnt by fire

Virgil (?)

To a master of mine,
Timothy John Crow

"Resting-state
is when the
brain is
resting."

Pieter Brugel the Elder, **The (Little) Tower of Babel**, 1563, *oil on panel,* Rotterdam, Museum Boijmans Van Beuningen.

SUMMARY

ABSTRACT

Introduction

A mood characterised by alternating mania and depression have been matter of curiosity and attention since ancient times.

According to T.J. Crow's theory on psychosis, Schizophrenia is strictly linked to the development of the faculty of language (begun in hominids from 6 to 4.2 million years ago) which depends by (anatomical and functional) asymmetry observable between the two cerebral hemispheres (Crow 2004).

Several data in the recent (and older) (Griesinger 1845) scientific literature support the hypothesis that schizophrenia and bipolar disorder are similar due to a large number of partially common features: symptomatology, genetics, cognitive features, neurobiology, connectivity alteration, etc..

A brief historical account about how often the classification of this disease changed across the last two centuries may suggest how the knowledge underling this diagnostic category is still fragile.

Aim of the research

The goal of this paper is to study Functional Connectivity (FC) among bipolar patients and to test the compatibility of Crow's paradigm with Bipolar Disorder, verifying the potential presence of hemispheric asymmetry alteration (left dominance deficit) through fMRI analysis.

Materials and Methods

18 outpatients of the Mood Disorders Unit at the Psychiatric Clinic of the University of Padua have been recruited. All subjects

had a diagnosis of Bipolar Disorder type I or type II, according to the criteria of the DSM-IV-TR).

16 healthy individuals were chosen matched for age, sex and education. Clinical and psychological conditions at the time of the experiment were investigated through some psychometric scales widely used for the evaluation of mood, anxiety and other psychopathologic aspects. All subjects underwent a MRI scan both in resting state and while they were attending two tasks: a phonemic (verbal fluency) exercise and a visuo-spatial test (mental rotations).

Results

From the neuropsychological point of view the phonemic task revealed no significant ($p<0.05$) differences between groups; on the contrary patients group showed decreased performance at the visuo-spatial task.

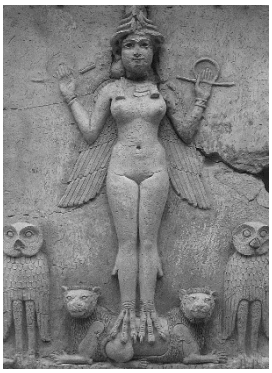
MRI FC was analysed using two different techniques. Independent Component Analysis (ICA) showed mainly a volume within the Dorsal Attention Network located in left Precuneus (Brodmann Area 7) where patient group presented a reduction of FC compared to controls. Graph analysis brought to light a number of inter-hemispheric and left intra-hemispheric connections revealed to be significantly less active in patients compared to controls, on the contrary substantial conservation of indices at the Network Level was observed.

INTRODUCTION

Bipolar Disorders: a brief history

§From ancient times to the age of Enlightenment

As far as we know the first human story describing a form of «cyclic mood» can be traced back to the Sumerian myth of "Inanna's Descent to Netherworld", where Dumuzi (the god-shepherd) had to lie for six months with Inanna (goddess of Fertility) and for the rest of the year with her *nemesis* sister Ereshkigal (goddess of the Underworld). Then most Middle-Eastern and Mediterranean civilisations developed similar myths such as the Roman "Rape of Proserpina" or its Greek ancestor "Persephone's *katabasis*" who – by eating six pomegranate (or opium)* seeds – condemned herself to spend every autumn and winter with Hades.



During the classic Greek age, and until the first century BC, the two polarities of the disorder were essentially always kept separate: depression, obviously associated with the concept of melancholy (from Greek μέλας "black" and χολή "gall", a concept so strictly intertwined with Hippocratic-Galenic Humor Theory) and that – much more vague but ever-lasting – of mania (literally μανία).

* Curiously poppy derivatives that were for the last millenniums the only antidepressant in the pharmacopoeia (even nowadays, e.g., buprenorphine with or without samidorphan).

Whilst the first concept signified basically the hyper-accumulation in the body of dark fluid (υγρος) and therefore always a disease, the second instead indicated generically the concept of *madness**. *Mania* (*Mana Genita* for the Romans) was the goddess of madness for the Etruscans and the θεία μανία (*«divine madness»*) was for the Greeks the moment when the sorcerer received the prophecy† from the deity.

In the first century BC, Virgil in the sixth book of the Aeneid still describes with these words the oracle of Delphi (that is, the Pythia):

> *"[To her who was talking in this way] suddenly, not her face, not a single color, or combed her hair remained, but the breathless chest and the wild heart swelled with anger, and she felt bigger and did not speak like a mortal, since it was expressed as being too close to power of the god's."*‡

Once again in Rome a few decades later (1st-2nd century AD) the Greek imperial physician Arethaeus of Cappadocia§ defined in the fifth chapter of *De causis et signis diuturnorum morborum* (On causes and signs of chronic diseases) mania as the

* In general terms μανία means "mental disorder" or "psychopathology", so much so that the same melancholy had the term λυπημανία (*lypemania*) as synonymous.

† See e.g. Socratic dialogues such as the Ion or Phaedrus by Plato. In the latter, for example, he wrote: "The greatest among the good things are given us through mania".

‡ "[…] ante fores subito non vultus, non color unus, / non comptae mansere comae; sed pectus anhelum, / et rabie fera corda tument, maiorque videri / nec mortale sonans, adflata est numine quando / iam propiore dei.[…]" . *Translated directly by the author of this thesis.*

§ He is famous especially for having made the term *"diabetes"*.

worsening of melancholy with which it forms an integral part of the same affection.

Except for sporadic exceptions* almost to the late eighteenth century, essentially in Europe depression and mania were considered – as result of the Hippocratic-Galenic system – as humoral imbalances determined by various etiologies, losing much the sense of the strong relationship between the two polarities of the disease.

Vincenzo Chiarugi (Empoli 1759 – Florence 1820) in his text *Della pazzia in genere e in ispecie* (About madness in general and in particular) came back to Aretaeus describing the manic ("[he/she] is like a tiger or a lion") as the opposite of melancholia and stated that between these ups and these downs there should be a close psychopathological relationship.

In the 18th century in Europe suddenly awakens the desire to focus and study this disturbance.

In 1845, the German psychiatrist Wilhelm Griesinger (Stuttgart 1817 – Berlin 1868), while directing the Department of Pathology at the University of Tubingen, called "usual" what would now be called *bipolar switch*, i.e. the sudden transition between melancholy and mania and also described a seasonality for this psychopathologic process†.

But the real breaking point was in 1851 when the French psychiatrist Jean-Pierre Falret (Marcilhac-sur-Célé, 1794-1870), director of the Salpêtrière hospital in Paris from 1831 to 1867,

* Rarely physicians in Modern Age medicine, such as Thomas Willis or Giovanbattista Morgagni, observed the sequential association of mania and melancholy.

† Griesinger W, "Pathologie und Therapie der psychischen Krankheiten", Krabbe, Stuttgart, 1845.

published the book *De la folie circulaire ou forme de maladie mentale caracterisée par alternative régulière de la manie et de la melancholie*[*]. In this volume for the first time the three basic elements (mood states) of modern bipolar disorder appeared and are organised in circles: every cycle is formed by depression, mania and free intervals[†] of possibly different duration and order.

§From the end of Folie Circulaire *to Manic-Depressive Psychosis*

Only three years later, in 1854, another French psychiatrist, Jules Gabriel Françoise Baillarger (Montbazon 1809 – Paris 1890), invented a just apparently overlapping expression: the *Folie á Double Forme*[‡].

Jules Baillarger – always very close to his master Esquirol[§] – was always very argumentative and aggressive against Falret, among mutual accusations of plagiarism, he objected precisely to the concept of "free interval", first denying its existence and then drastically diminishing its importance. Even nowadays some authors

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[*] "On circular insanity or a form of mental illness characterised by the regular alternation of mania and melancholy" is a quite brief text (14 paragraphs) originally published on the *Gazette des Hospitaux* in 1851.

[†] This (genial) concept will become the apple of discord for much of the psychiatry of bipolar disorders of the second half of the nineteenth century.

[‡] Baillarger JGF, *De la folie á double forme*, Ann Méd-psychol 1854;6:369-89.

[§] Jean-Étienne Dominique Esquirol (Tolouse 1772 – Paris 1840) was one of the greatest French psychiatrists of all times. Philippe Pinel's pupil at Salpêtrière, he was the most important maker of the medicalisation of mental illness in France and then throughout Europe.

suggest that the expressions *folie circulaire* and *folie á double forme* could still be useful to indicate respectively bipolar disorders with and without free intervals between episodes (Azorin *et al.* 2011).

In essence, however, the concept of *circular insanity*, after having coexisted in France for some luster with *double-form insanity*, «broke out» throughout continental Europe, thanks also to the importation into Germany by Karl Kahlbaum* of the (equivalent) concept of *circuläres Irreisen*, then in the Anglo-Saxon countries in Europe and overseas.

At the end of the 19th century†, the father of modern German

psychiatry Emil Kraepelin (Neustrelitz 1856 – Munich, 1926) put a cornerstone of his new nosology of mental diseases on the distinction – amongendogenous psychoses – between *dementia praecox* and precisely *depressive mania*. Substantially this second diagnostic category was the fusion of those of circular insanity and unipolar depression (or melancholy).

This concept probably represented historically the embryo of the *continuum* theory, nevertheless Kraepelin himself criticised this

* Karl Ludwig Kahlbaum (Drezdenko 1828 – Görlitz 1899), German psychiatrist, he wrote the volume "Grouping and Classification of Mental Illnesses" (*"Die Gruppierung der psychischen Krankheiten und die Einteilung der Seelenstörungen"*, Kafemann, Gdansk, 1863). He always standed in favor of Falret's position and against Baillarger's one.

† The turning point is generally referred to as "The Clinical Position of Melancholy" (Kraepelin E, *Die klinische Stellung der Melancholie*, Mschr Psychiatr Neurol. 1899;6:325-35).

classification entity especially after the Great War* when he stated he was looking for new nosographic solutions to it.

§From criticisms to Kraepelin to Bipolar Disorder

Even if a few European countries remained largely unrelated to the Kraepelin's reform of manic-depressive psychosis, in the rest of the continent, this concept spread very rapidly, destined to persist.

Nevertheless, the first germs of criticism emerged immediately (in the first years of the 20th century) with the first subdivisions of melancholy (in: affective, depressive, agitated, astonished and hypocondriac) by Carl Wernicke (Tarnowskie Góry 1848 – Gräfenroda 1905). But a colleague of his in Halle contrasted most with his theories: Karl Kleist (Mulhouse 1879 – Frankfurt am Main 1960) began to differentiate affective disorders into two groups *unipolar* (einpolig) and *bipolar* (zweipolig)†.

The massive introduction and dissemination to the major international psychiatrists of the concept of bipolar disorder is, however, starting from 1966, when the Italian psychiatrist – but based in Sweden – Carlo Perris (Cosenza 1928 – Umeå 2000) writes a series of eleven papers as supplements to *Acta Psychiatrica Scandinavica* all entitled: "A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses" (Perris 1966).

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* "Phenomenology of insanities" (Kraepelin E., *Die Erscheinungsformen des Irreseins*, Z Gesamt Neurol Psychiatrie, 1920;62:1-29).

† It is important to underline that both Kleist and Wernicke never considered *pure* mania such as something compulsorily or even intrinsically linked to bipolar disorders, as it is in the latest editions of the DSM.

A similar study was carried out by Jules Angst at Burghölzli in Zurich between 1959 and 1963, with similar results (Angst and Perris 1968). What came out from these studies was that patients suffering from "unipolar mania" were genetically extremely close to those with bipolarity, so to say that the first category (the old *pure mania*) could be considered simply an artifact.

§Back to «Einheitpsychose»?

The concept of spectrum in psychiatry dates back to the 20s of the past century, with almost contemporary formulations by two great psychiatrists of the twentieth century: Ernst Kretschmer (Wüstenrot 1888 – Tubinga 1964) and Eugen Bleuler (Zollikon 1857 –1939).

But probably the first strong clinical application has been to attribute – since the late 1970s (Akiskal *et al.* 1977) – to the Armenian-Lebanese psychiatrist Hagop Akiskal (Beirut 1944 –). He categorised Bipolar Disorders on the basis not just the intensity of mania but also the temporal pattern of the different phases. He also analysed the relationship between bipolarity and creativity, for the first time explicitly expressing the idea of the existence of a *continuum* ranging from depression to mania. Obviously a return to Kraepelin.

As we will see later for other contemporary psychiatrists such as T.J. Crow (Oxford) or German Berrios (Cambridge), that continuum (and therefore its spectrum) would extend for much of the old DSM-IV axis including not only mood disorders, but also all psychotic diseases including schizophrenia. Here the return seems rather to the concept of unique psychosis expressed by Griesinger*.

This latter position seems to have been substantially accepted also by the latest version of DSM (DSM-5) as the bipolar disorder now no longer mingles with mood disorders (as it was but in DSM-IV – *Kraepelin-Akiskal*), but in a "Bipolar and Related Disorders" between "Schizophrenia Spectrum and Other Psychotic Disorders" and "Depressive Disorders" (*Griesinger-Crow*).

* The concept of *unique psychosis* (Einheitpsychose) was first put forward by Wilhelm Griesinger in the 'Year of Rebellions' 1848, "according to which all mental illnesses represent levels of increasing severity of the same basic disorder, which are stages or phases; this conception brought much success to Griesinger so he was called to the Medical Clinic Chair in Zurich and headed to the Burghölzli where the birth of schizophrenia will take place" (see Migone P, *Storia della schizofrenia – I parte*, Il Ruolo Terapeutico, 2012;119:67-78.).

*Bipolar Disorders: epidemiology**

The most recent reliable epidemiological data on Bipolar Disorder worldwide (Merikangas *et al.* 2011) reported a lifetime prevalence of 0.6% and 0.4% a year for Bipolar Bisorder Type I (BD1), 0.4% and 0.3% respectively for Bipolar Disorder Type II (BD2) and 1.4% and 0.8% for sub-threshold hypomania (sthm) respectively. Type I showed the highest lifetime prevalence in male, on the other hand Type II was more frequent in the female gender, while no correlation with other socio-demographic variables such as marital status, work and income.

The age of onset for more than 50% of subjects considered was less than 25 years. There were also significant differences between the various geographical areas, with an apparently higher prevalence (of the whole spectrum) in the more industrialised nations (highest: US 4.4%) and lower in poor countries (lowest: India 0.1%), but maybe there is an under-diagnosis bias in some underdeveloped countries (and perhaps over-diagnosis bias in some of the richest ones). For other studies, prevalence rates are slightly lower (~0.75% mean pooled, ~0.85% at 6/12 months) (Ferrari, Baxter and Whiteford 2011).

Although the prevalence of this disease is significantly lower than that of other psychopathologies such as depression, Bipolar Disorder is a major social problem for current civilisations. Indeed, in the latest Global Burden of Disease, the World Health Organization reports BD as the sixth absolute factor among the

* Unless otherwise specified, this section refers to DSM-IV-TR (and not DSM-5) since diagnoses of experimental part were made based on 'old' criteria.

disabling mental illnesses (Disability-Adjusted Life Year, i.e. the sum of years lost for mortality and disability); then, comparing the geographical distribution of the prevalence, the map (of the DALY) is quite different (see *Fig. 1*).

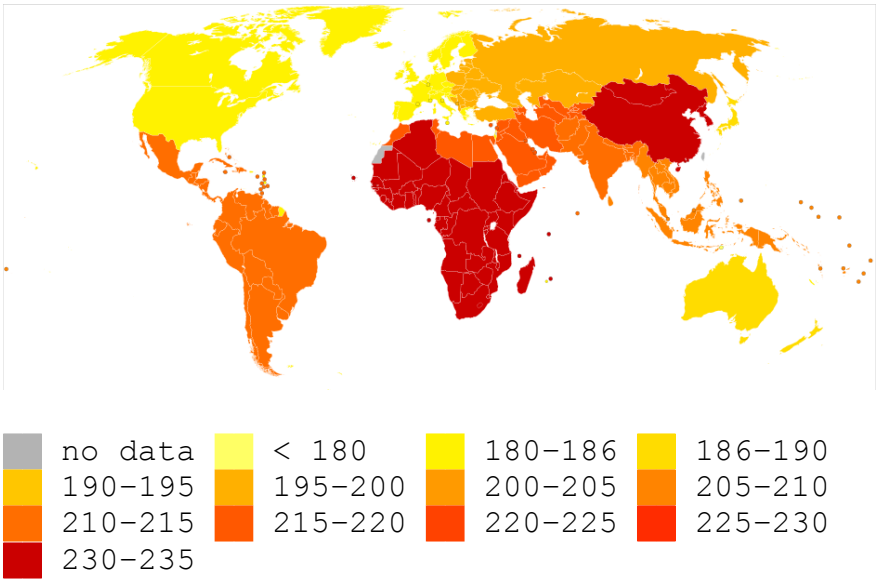

Figure 1. ***DALY for Bipolar Disorder*** *(for 100.000 people).*

Finally, patients with bipolar disorder have a considerably higher mortality rate than the general population, as well as suicidal risk per se (relative risk of 15.0 for males and 22.4 for females) and for other causes (RR=2.0) (Osby *et al.* 2001). Furthermore a higher prevalence of organic comorbidity associated mainly with metabolic syndrome (diabetes, hyperlipidemia, cardiovascular diseases...) was found (Laursen, Munk-Olsen and Gasse 2011).

Bipolar Disorders: clinics

*§Notes of psychopathology**

The classic division into subtypes of mood disorders is based on the course: unipolar disorders, characterised by the exclusive occurrence of depressive episodes, and bipolar disorders, characterised by the alternation of manic, hypomanic or mixed episodes and depressive episodes. Longitudinal aspects represent the distinctive feature of mood pathology and are basic to diagnosis, prognosis and planning of therapeutic intervention. DSM-IV-TR (APA 2000) distinguishes bipolar disorders in Bipolar Disorder Type I, Bipolar Disorder Type II and Cyclothymia.

The main characteristic of Bipolar Disorder Type I is the presence of one or more manic or mixed episodes, generally alternating with depressive episodes, including patients with only manic attacks (5-9%). Bipolar Disorder Type II includes patients who have at least one major depressive episode and at least one hypomanic episode. Cyclothymia is characterised by a rapid and continuous (for at least two years according to the DSM) alternation of depressive and hypomanic phases of mild to moderate intensity, however, not satisfying criteria for the full manic or depressive episode. If mood alteration was attributed to the physiological effects of a substance of abuse (e.g. cocaine, methamphetamine ...), to side effects of some drugs (e.g. antidepressants, antiparkinsonians, corticosteroids...) or to another medical condition no disorder of the

* Unless otherwise specified, this section refers to DSM-IV-TR (and not DSM-5) since diagnoses of experimental part were made based on 'old' criteria.

bipolar spectrum could be diagnosed.

From the DSM-5 (APA 2013), however, it is possible to diagnose a hypomanic or a manic episode occurring during an antidepressant treatment (with drugs or physical therapies – e.g. ECT) in case the syndrome framework is observed even after the physiological effects of treatment.

WHO classification (ICD-10) (WHO 2008) places Bipolar Disorder in the chapter of mood disorders, together with depressive disorders, but does not provide for the distinction between Type I and Type II.

Therefore we can conclude that the psychopathologic elements that may constitute Bipolar Disorders are four: depressive episodes, manic/hypomanic episodes, free intervals and mixed states. Whilst depressive or (hypo)manic states (within BDs) have been nosographically enough stable for several decades, the debate on the latter has been quite lively.

Mixed episodes, though had been described – even if probably without full comprehension – by physicians of classical age such as Hippocrates (Kos 460 – Larissa 377 BC) or the aforementioned Aretaeus of Cappadocia, were certainly identified at least from the Eighteenth century by great modern clinicians, such as Boissers de

Sauvages* and William Cullen†. They described and classified "oxymoronic" kinds of melancholy, such as *m. moria*, *m. saltans*, *m. errabunda*, *m. silvestris*, *m. enthusiastica*, etc.. Nevertheless at the beginning of the nineteenth century, Johann Heinroth‡ formulated a new psychiatric nosography (Heinroth 1818) where the so-called "hyper-asthenias" (i.e. "a mixed form of exaltation and depression or weakness", i.e. mixed states) classified into three groups: *animi morbi complicati*, *morbi mentis mixti* e *morbis voluntati mixti* (or *athymia*) – each then divided into four different pathologies.

At last, Kraepelin and others built the current framework for classical mixed states: they described clinical entities where mood, ideation, and psychomotor tones were altered in the opposite direction (e.g. mood depressed with psychomotor agitation and ideational acceleration) (Jaspers 1959).

More than 50% of these patients have psychotic symptoms, such as delusions, auditory hallucinations and loosening of associative

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* François Boissers de Sauvages de Lacroix (Alès 1706 – Montpellier 1767) was a French physician and botanist famous for his ponderous (for the time) all-embracing classification system of human diseases. This nosography – which many were considered to be the plastic implementation of the first thought of the great Oxfordian physician Thomas Sydenham (Wynford Eagle 1624 – Pall Mall 1689) – included 295 *genera* (classes of pathologies) and 2400 *species* (single disorders).

† William Cullen (Hamilton 1710 – Kirknewton 1790) was a Scottish physician, philanthropist and scholar, a great theorist of "*nervous energy* as a source of life" and "muscles as a prolongation of the nerves"; he was the first to think that the etiology of *neuroses* were not to be sought in the "disequilibrium of *humors*", but in the nervous system itself.

‡ Johann Christian August Heinroth (Leipzig 1773 - 1843) was a German psychiatrist (the first in Germany to sit on a chair of *mental pathology* – at University of Leipzig), famous especially for inventing the word *psychosomatics*.

links. Mixed states are present in a considerable part (30-40%) of bipolar patients; they are more common in women than in men and are associated with early onset, increased severity of disease, higher frequency of recurrences and reduced response to treatments. The most serious complication has been recognised in the very high suicidal risk (estimated about 25-50%).

The DSM-IV-TR (APA 2000) provided the possibility to diagnose a mixed episode in the event that, at least during one week, both the maniac episode and the depressive episode were met together. On the contrary, in the DSM-5 (APA 2013) this diagnosis disappears, leaving the possibility of using the expression "with mixed features" (in case during a manic, hypomanic or depressive episode, there are at least three criteria of the opposite mood state*).

§Notes of therapy

Treatment of bipolar disorder is mainly pharmacological. The first substance able to really change the life of people affected by BDs is still the gold standard and it are *lithium salts* (above all carbonate).

Mood stabilisers

The medical use of these molecules was serendipitously discovered between the late 1940s and early 1950s (Cade 1949) by the Australian psychiatrist John Cade (Murtoa 1912 – Victoria 1980) and introduced into clinical practice by his Danish colleague Mogens Schou (Copenhagen 1918 – 2005).

* The DSM-5 also states that if criteria both for manic and depressive episode meet at the same time, the correct diagnosis is "maniac episode with mixed features".

Carbolithium exhibits proofed efficacy both in the prevention of acute mania and in maintenance treatment, as well as in the prevention of suicidal behaviour. Lithium appears to be more effective for euphoric mania while it is less effective for depressed or mixed episodes or in rapid cycling. The main practical limit to its use is given by the very narrow therapeutic window and therefore by the need to monitor its plasma levels both to avoid the risk of intoxication and to verify that plasma concentration reaches an effective level.

The most common side effects are weight gain, tremors, nausea, increased urination. Lithium can reduce thyroid and renal function (during long-term treatment this is almost normal), therefore periodic checks are required. Excretion is purely renal, therefore there is no hepatotoxicity. A peculiar effect is the reduction of effectiveness after retraction after suspension.

Lithium carbonate is one of the so-called *mood stabilisers*. According to some neuropsychopharmacologists, lithium salts would represent the only proper mood stabiliser, since all others are antiepileptic drugs (AEDs), too[*]. Those mainly used are:

- *Valproate* (valproic acid, sodium valproate, magnesium valproate), such as lithium, is active above all on mania (even if it is weakly depressing) and needs periodic hematochemical monitoring. Contrary to lithium, however, it is effective on acute mania (loading dose), dysphoric mania, and rapid cycling. Common side effects can be: sedation, weight gain, gastrointestinal disorders.

[*] It is interesting to note that almost all anticonvulsivants also work as mood stabilisers. This effect indeed usually sought after by psychiatrists is nothing more than a side effect for neurologists (*affective flattening*).

Poor hepatotoxicity.

- *Lamotrigine*, like lithium, has poor usefulness in acute phases because it requires extremely slow titration (crucial to avoid the most common side effect, i.e., rush, along with headache, visual disorder and dizziness). But differently from other drugs it is very effective in preventing depressive episodes (even in recurrent unipolar depression) and poor on mania and hypomania.
- *Carbamazepine* and *oxcarbazepine* are used above all because of their effectiveness on euphoric mania and mixed states. The very poor preventive capacity, the bad profile of the interactions and the adverse effects (typical of the older anti-epileptic) currently largely limits their use.
- *Topiramate*.
- *Gabapentin*.

Antipsychotic drugs

The use in clinical practice of *first-generation antipsychotic* drugs (such as haloperidol or chlorpromazine) has been almost completely abandoned – at least in rich countries – also for the treatment of acute mania due to their depressed, neurotoxic, cardiotoxic and extrapyramidal effects.

The use of *atypical antipsychotics*, however, is highly debated (especially because of their real preventing capacity towards the two poles) but currently some of these molecules are frequently included in the list of drugs prescribed in the treatment of bipolar disorder together with the most common mood stabilizers (lithium + new

generation AEDs). Main are[*]: *Aripiprazole*, *Asenapine*, *Iloperidone*, *Lurasidone*, *Olanzapine*, *Paliperidone*, *Quetiapine*, *Risperidone*, *Ziprasidone*.

Antidepressant drugs

The use of antidepressant drugs (ADs) is, if possible, even more controversial beyond the obvious risk of inducing a switch to mania[†].

Current trends are to avoid always the use of TCAs (as well as of iMAOs), and to use other classes (such as SSRIs, SNRIs, NDRIs, NaRIs, NaSSAs) as monotherapy or with mood stabilisers.

Finally the use substances with melatoninergic activity (currently substantially *agomelatine*), able of influencing (positively) circadian rhythms, seems still promising.

Psychotherapy

It is current common opinion that psychotherapy can be a good adjuvant strategy for the treatment of bipolar disorder.

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[*] *Asenapine* within EU has been approved only for the treatment of mania (BD1). *Iloperidone* marketing in EU has been refused by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency's (EMA).
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004149/smops/Negative/human_smop_001181.jsp&mid=WC0b01ac058001d127.

[†] Since the 1970s, when it was observed that – especially in young bipolar patients, antidepressant administration has been accused of increasing the risk of psychosis, up to the Post's classic observations (kindling model) (Post 1992) (see *Fig.2*), so the use of antidepressants (especially as single drug) in bipolar patients would promote progression to rapid/ultra-rapid cycling.

According to Robert Post (Post 1992) (see *Fig. 2*) several

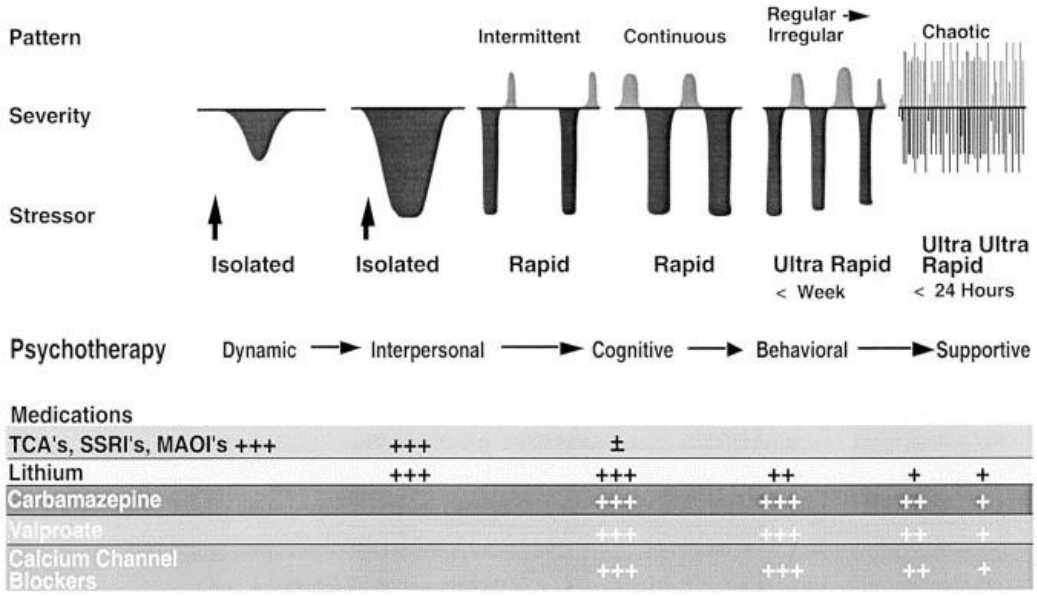

Figure 2. ***Post's kindling phenomenon in bipolarism.*** (Post 1992)

psychotherapies have proved useful: in the early stages psychodynamic and interpersonal therapies, then cognitive-behavioral and behavioral therapies, and finally the supportive ones.

Since the 1990s, however, a specific approach to bipolar disorder has been spread (in Europe – mainly thanks to the Catalan psychiatrist Edmund Vieta – and in other Anglo-Saxon countries): *psychoeducation*. Nowadays this technique is widely believed to be one of the most effective on BDs (also because of its high degree of integration with other therapies, e.g. the pharmacological one) (Vieta *et al.* 2005). This evidence-based method consists essentially of training of patients and their social environment (families, partners, friends, etc.). The main aim is to prevent recurrences (or at least identifying them as soon as possible), to promote the return of the patient to everyday life after the polar episodes and to improve the quality of life of families by supporting them, above all informing and providing them a chance to debate and developing strategies for

managing “difficult moments”.

Another specific psychotherapeutic approach to BDs is represented by *Social Rhythm Psychotherapy* (a kind of interpersonal psychotherapy), which puts the so-called *social stabilisers* hypothesis as a specific basis. Opposed to *stressful events* – these elements (such as routine activities or social duties) should be protective against mood oscillations and they could therefore be used to stabilise and regularise biological clock.

Bipolar Disorders: neurobiology

As noted in the first chapter since the classical age, the most widespread interpretations of the aetiology of bipolarity were already based on hypotheses that in the 20th century would have been define *biologicist*. Both the current expressions *“humour”* and *“thymic state”*[*] came from that past, a time ruled by the “doctrine of *cells*” (that nowadays we would call “ventricles”). Therefore, as already noticed (see above), depression *(melancholy)* was basically considered to be the symptomatic expression of humor imbalance *(dyscrasia)* with increased black bile (*atra bilis*), while – not always – it was believed that mania was caused instead by a yellow bile hoard.

Since the early ’1950s – more or less since the discovery of lithium salts – neurobiological research on bipolar disorder has been focusing on analysis of alterations in the following fields of

[*] Until the end of Middle ages thymus was believed to be a *humor*-secreting gland (and of course not having the function to specialise T-lymphocytes).

investigation: brain structure, functionality cerebral function, neurotransmitter function, endocrine system, immune system, neurophysiology, chronobiology. For reasons of brevity, only a very brief excursus will be made in this short treatise.

The most widespread etiopathogenetic model nowadays is the so-called *vulnerability-stress model*: subjects with a variable genetic-based vulnerability in mood regulation systems (or other related deficits) would be at risk of developing the disorder following exposure to triggering events (physical stress or psychological).

§Notes of genetics

Since the late 1950s (at the time of the aforementioned studies by Perris and Angst) genetic research on manic-depressive psychosis has been giving good results. Even today, the international scientific community attributes to familiarity – and especially to the genetic component – great importance in the etiopathogenesis of BDs. Indeed very replicated papers in literature – e.g. (Mortensen *et al.* 2003) – found that first-degree relatives of patients affected by BD1 (Invernizzi 2006) have a risk of 8 to 18 times greater than that of the general population of being affected by the same disorder, and a relative risk of 2-10 developing Major Depression Disorder (MDD). The children of a bipolar patient (Type I, BD1) have a 25% risk of develop the same pathology, with a probability rising to 50% whether both parents are affected*. Monozygotic twin studies showed a

* These percentages, together with the failure of linkage studies, seem to evoke the – maybe old-fashioned but evergreen ad still promising – idea of a monogenic (~Mendelian) alteration (Crow 2007).

concordance of 33-90% (in particular with regard to BD1), compared to 10-25% of dizygotic twins.

The most likely candidate chromosomes responsible for the genetic part of the disease are currently: 5 (e.g. Crowe & Vieland 1999), 11 (e.g. Rietschel et al. 2011), 12 and X.

In the last decade, initial enthusiasm was triggered by the so-called GWAS (Genome-Wide Association Studies) that allowed to identify multiple SNPs (Single Nucleotide Polymorphisms) associated with bipolar disorder; currently the most studied genes are (Craddock and Sklar 2013)(Kato 2007):

- CACNA1C* *(12p13.33)* encoding for voltage-dependent calcium channels and ANK3 (10q21.2)† encoding for *Ankyrin-G* (nodes of Ranvier). Voltage-dependent (calcium and sodium) channels of neuron membranes (Ferreira *et al.* 2008);
- ODZ4 (or TENM4‡) *(11q14.1)*, encoding for *Teneurin-4* (transmembrane protein). Perhaps involved in *reward* processing;
- NCAN§ *(19p13.11)*, coding for *Chondroitin Sulfate Proteoglycan-3 (Cspg3)* that mediates cell adhesion and migration;
- P2RX7** *(12q24.31)*, encoding for the *purinoceptor P2X (ligand-gated ion channel)*, (Barden *et al.* 2006);

* http://www.omim.org/entry/114205

† http://www.omim.org/entry/600465

‡ http://www.omim.org/entry/610084

§ http://www.omim.org/entry/600826

** http://www.omim.org/entry/602566

- PCDH11X/Y[*] *(Xq21.31-32/Yp11.2)*, two genes encoding for *protocadherins 11 X* and *Y*, probably responsible for branching of dendrites and maybe axons (Zhu *et al.* 2012). According to TJ Crow, the duplication of this gene (from chromosome X to chromosome Y), occurring in hominids (Australopitheci) between 6 and 4.2 million years ago, is responsible for both the large cerebral (hemispheric) asymmetry in modern homo sapiens and the faculty of language.

§Brief notes of endocrinology and inflammation

The close link between the **endocrine balance** and the mood (and related disorders) has been clarified long time ago in both directions: both hormonal alterations resulting from affective diseases and mood problems resulting from endocrine disorders.

By extremely simplifying it, it is possible to say that the centre of reciprocal influence between endocrinology and psychiatry is the "limbus-hypothalamus-hypophysis-adrenal axis" (McEwen 2000).

The relationship between **inflammation** and mood disorders has also been widely investigated over the last few years, and the almost invariably identified relationship sees a link between increasing inflammatory indices on the one hand and the onset and deterioration of both MDD and BD from the other[†].

[*] http://www.omim.org/entry/300246 & http://www.omim.org/entry/400022

[†] E.g. the increasing concentration of inflammation markers (PGE2, PCR, TNF-α, IL-1ß, IL-2 and IL-6) in peripheral blood and cephalide-rachid liquor (Dickerson *et al.* 2013).

The appearance of mood symptoms during pro-inflammatory therapies (predominantly for antiviral purposes, e.g. IFNγ) is so frequent that in some specialist centers* for nearly two decades it has been directly administered SSRI (or other antidepressant) even before a clinical deflection of the mood tone could be detected.

At the moment many authors argue that also *inflammation and mood are bidirectionally related* (Raison and Miller 2013). Therefore, recently a big debate began on the use of anti-inflammatory drugs of various kinds for treating mood (and anxiety) disorders NSAIDs, steroids, biological drugs, antibiotics, direct antioxidants, antioxidant co-factors such as N-acetylcysteine, etc. (Rosenblat *et al.* 2014)†.

§Brief notes of chronobiology

Chronobiology (Greek: *χρόνος time*, *βίος life* and *λόγος reasoning*) is one of the most promising fields of interest for the study of BD.

Clinically, in addition to the well-known alterations of the sleep-wake rhythm present during the episodes of disease (both manic and depressive) most patients have an altered chronobiological pattern‡ even during free intervals, with high frequency of *evening chronotype*§, instability in circadian rhythm and reduced sleep

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* Such as the hospital *Germans Trias i Pujol* (UAB) of Barcelona.

† About this issue, for reasons of brevity, please refer to the following submitted paper: Padovan G et al, High Sensitivity C-Reactive Protein as a potential biomarker of neuroinflammation in psychiatry, *Curr Psych Rev.*

‡ Like the terms *genome* and *proteome*, also the word *chronome* exists and stands for the structural set of cycles and biological rhythms characterising a given individual.

§ See e.g. the *Morningness-Eveningness Questionnaire* (Horne and Östberg 1976).

quality. It has been suggested that chronobiological alterations are present long before the onset of the disease, thus constituting a possible marker for the population at risk. Recently, the interest of the scientific community in the chronobiological study of mood disorders has been further increased by the production of new drugs capable of acting specifically and significantly on circadian cycles (especially melatonergic antidepressants) and the spread of psychotherapies such as the aforementioned based on social rhythms.

§Notes on structural and functional alterations[*]

From a **structural** point of view, the most recent meta-analyses have been carried out mainly from voxel-based morphometry studies, mainly because of its greater simplicity in the metanalytic comparison compared with other automatic analyses, such as surface-based morphometry or deformation-based morphometry, and especially semi-automatic techniques.

At the moment probably the only observation common to all the latest meta-analyses is that of the volume reduction of right insula (Ellison-Wright and Bullmore 2010; Houenou *et al.* 2011; Delvecchio *et al.* 2012; Selvaraj *et al.* 2012).

From a **functional** point of view, findings seem to be even fewer at this moment probably because meta-analyses in this field are very hard, having to handle the bias of the various tasks (a part from

[*] *The huge amount of data published almost weekly about this issue, makes it impossible to write a paragraph that may have the far-off claim to be exhaustive. For this reason just a really quick review of gross generalities will be wrote.*

resting state studies). Here is a rather recent meta-analysis (Lindquist *et al.* 2015) which is – meaningfully – inconclusive.

A new and fascinating field of investigation, currently in great expansion, is that of structural and functional (resting state) **connectivity** studies that seem very promising, but – precisely because of the great current activity – it is very difficult to make a precise and synthetic point of the situation.

The only common trait between the paired studies that (maybe) can be identified now could be the failure to inactivate a particular resting circuit (*DMN - Default Mode Network*) after several linguistic tasks (most often fluency)*. A brief bibliography: (Favre *et al.* 2013) (Liu *et al.* 2015) (Wang *et al.* 2015) (Redlich *et al.* 2015) (Başar *et al.* 2015) (Goodkind *et al.* 2015) (Altshuler and Townsend 2012).

§Notes on cognition

The decline in *working memory* is commonly accepted as a fact in the depressive phase, but according to some authors (eg Clark & Goodwin 2004) it would not only be present in patients with good (or excellent) functioning, but it would be pre-existing, persistent and without correlation with any residual symptoms, but worse in the acute stages of the disease.

In recent years, some authors pervade the cause of the possible existence of a peculiar *cognitive endophenotype* of BDs. This would be confirmed by the presence of cognitive impairment also in relatives:

* Therefore both verbal and executive functions at once. But even in this case there is at least one study contradicting this evidence (Yoshimura *et al.* 2014).

a meta-analysis (Bora, Yucel and Pantelis 2009) found possible endophenotypes present in stable form in patients and their non-affected first-degree relatives (response inhibition, set shifting, verbal memory and target detection). Other author point out the *creativity* as main cognitive feature of BDs (especially BD2) (e.g. Hagop Akiskal).

Hemispheric lateralisation in psychoses

§Notes of physiology of brain asymmetry: from Yakovlev to Geschwind

Since the discovery of the two main language areas by Paul Pierre Broca (1824-1880) in 1861 and Carl Wernicke (1848-1905) in 1874 (Masdeu 2000; Eling and Whitaker 2009), the lateralisation of – at least – some mental faculties in the encephalon are lateralised have been almost suddenly proofed by Broca himself in 1871 (Stone 1991). But probably the general agreement on the fact that the physiologic brain (above all its cortex) is lateralised, not only functionally but also structurally, was due mainly to the description of the first important cortical anatomic asymmetries in the normal brain. This happened during the sixties in Boston (Yakovlev and Rakic 1966) by the Russian physician Paul Ivan Yakovlev (1894–1983) (Lecours 1989). Yakovlevian torque is briefly explained in →*Fig. 3*, its implications on language centres summarised in →*Fig. 2*. Nowadays brain asymmetry in Homo sapiens is widely studied as a biological phenomenon (*see e.g.* Toga and Thompson, 2003) connected with human mental higher functions.

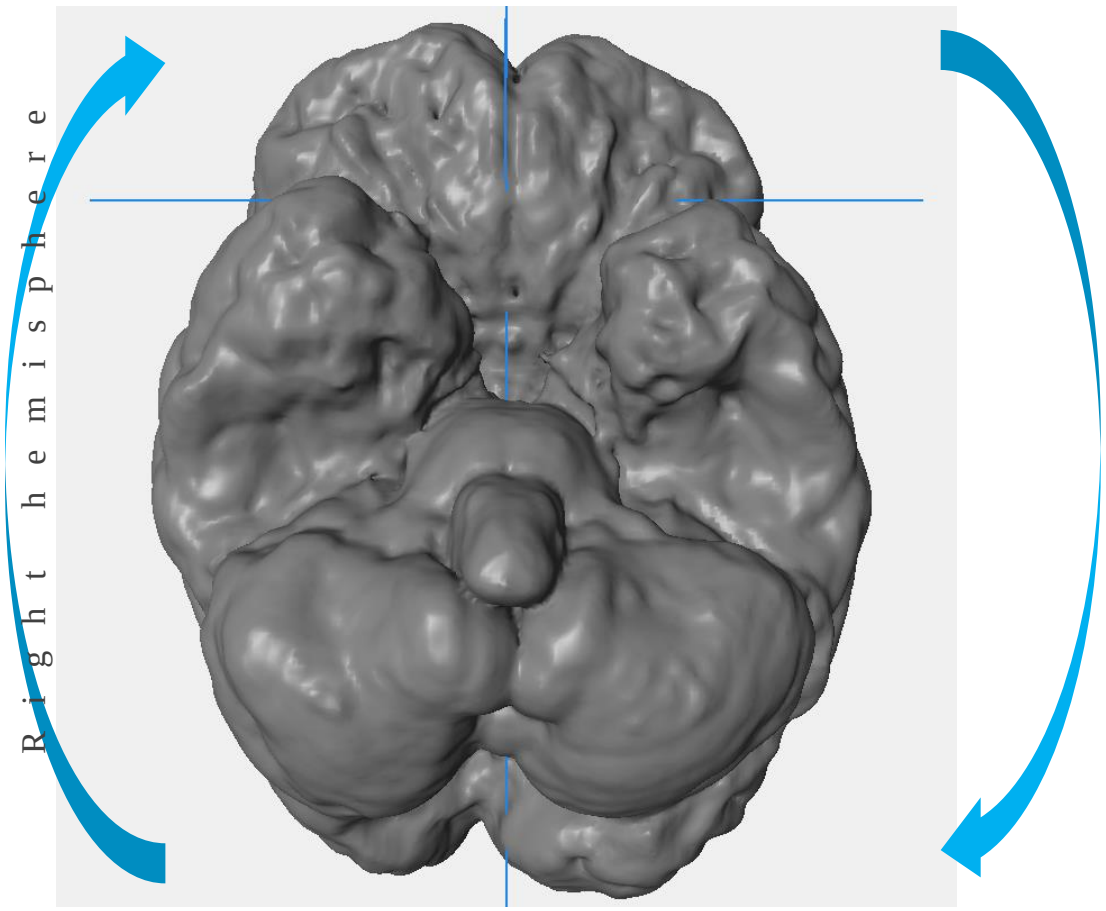

Figure 3. ***Brain asymmetry and Yakovlevian torque.*** This 3D picture was built from an *in vivo* MRI scan of a healthy sample subject (without modifications for enhancing asymmetries) using Multi-Image Analysis GUI software (Mango® – RII, UTHSA) (Lancaster *et al.* 2012).

As you may see from this reconstruction of the caudal surface of the encephalon (pictured with the axes of a hypothetical perfect sagittal symmetry) this physiological phenomenon brings about a clockwise twist of the brain described over axial plane, from a bottom-up perspective. This implies several features concerning the asymmetry of human brain cortex. The most evident are represented by the tendency of the most anterior portion of right frontal lobe to protrude at the front (compared to the left one) and to move to the middle, often crossing the mid-sagittal plane (as well as at occipital level we have the opposite situation: left hemisphere leans over backwards and moves to the right). A simple way to describe brain torque variability is studying volume distribution ('volume torque') which is able to show both: "hemisphere shift and differential tissue distribution within the hemispheres" (Chance, Esiri and Crow 2005). This shows that there are two components in brain torque: the first is the hemisphere shift and the second is the differential tissue distribution within the hemispheres.

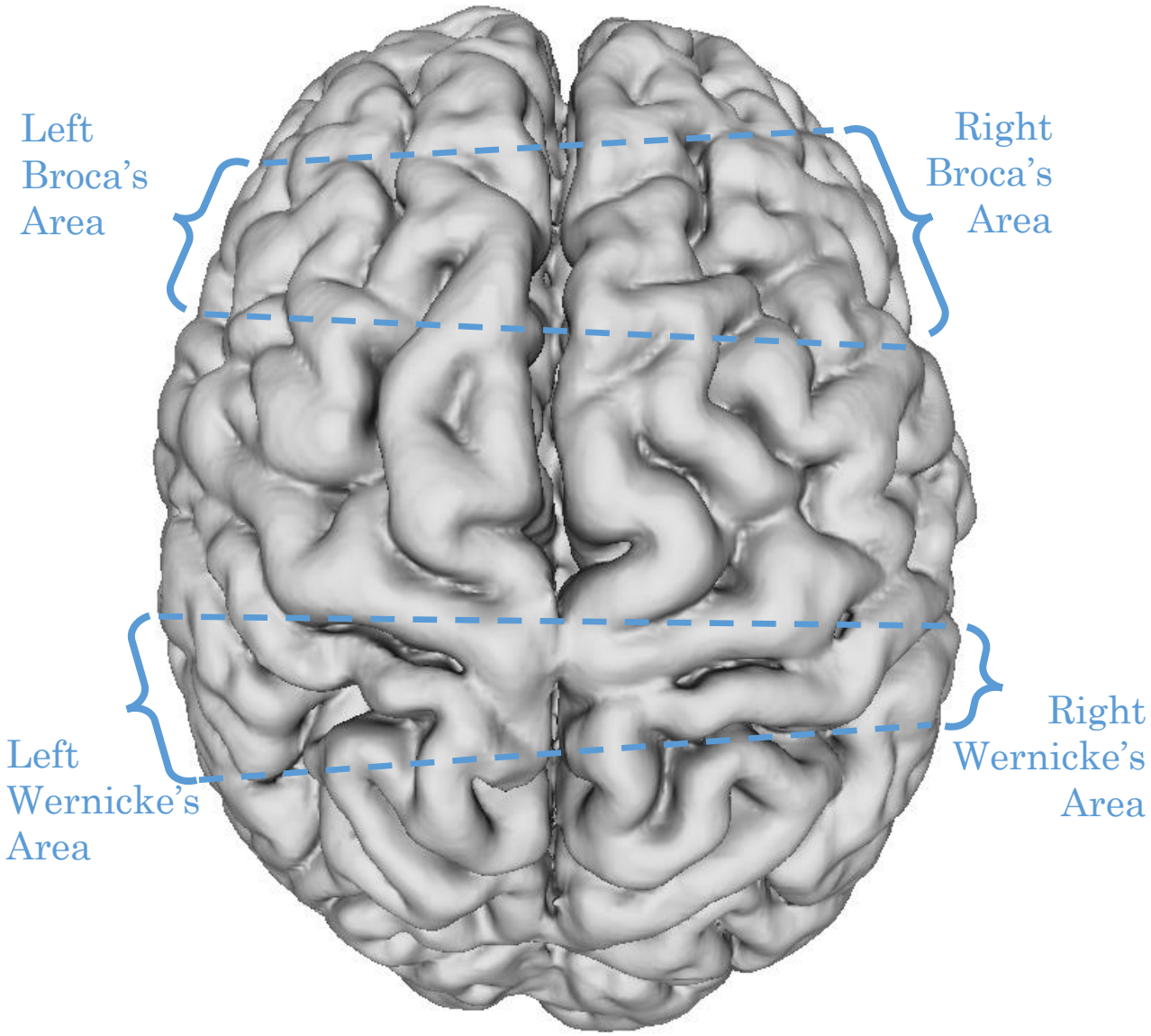

Figure 4. ***Asymmetry of language areas.*** The effect of Yakovlevian torque on main language cortical centres does so that Broca's area is usually wider at left compared to right, while Wernicke's area is narrower at left (Crow 1998).

[These 3D pictures were built by the candidate from an *in vivo* MRI scan of a healthy sample subject (without modifications for enhancing asymmetries) using Multi-Image Analysis GUI software (Mango® – RII, UTHSA). See also *Fig.3*].

After Yakovlev there were other anatomical observations in this sense (for example, the so-called *Ruben's phenomenon* on Sylvian fissure lateralisation pattern).

Another author – Norman Geschwind – must be mentioned for the discovery of the physiological asymmetry of planum temporale (PT) (Geschwind and Levitsky 1968), that is now an absolutely established fact (Oertel-Knöchel *et al.* 2013). Interestingly even this finding is strictly linked to language – being PT part of Wernicke's area – and it is also connected with sensorimotor lateralisation, sure enough reduced leftward asymmetry of PT correlates with higher probability of left-handedness (Steinmetz *et al.* 1991) whilst enhanced leftward asymmetry of PT is often present among "musicians with perfect pitch display" (Steinmetz 1996).

Another physiological consideration is that brain asymmetry seems to be one of the most clear features differentiating Homo sapiens from other animals (including big apes)*.

§Notes of pathology of brain asymmetry: Crow's theory on the origin of schizophrenia

Historically probably the first link between non-physiologic cerebral asymmetry and (chronic†) neuropsychopathology was the

* A research – about to be published but recently accepted – by TJ Crow, Neil Roberts (CRIC - University of Edinburgh), Lily Xiang et al., which compares MRI brain images of 80 chimpanzees to as many human subjects, finds an asymmetry of the candidate areas of Pan troglodytes two or three orders of magnitude lower than Homo sapiens.

† Discussing about acute diseases, as already mentioned, Paul Broca in 1871 performed a craniotomy to drain an epidural abscess that was causing a non-fluent aphasia (Stone 1991).

observation that autistic patients present usually an over-lateralised brain (Hier, LeMay and Rosenberger 1979; McManus and Bryden 1991).

In the late eighties TJ Crow hypothesised that schizophrenia were caused by a deficit of left cortex dominance for language (Crow *et al.* 1989) due to altered (reduced) asymmetry (Crow 1997). One of the major advantages of this theory is that it gives an evolutionary explanation about the permanence of schizophrenia among populations. It appears as a genetic characteristic indeed, as a matter of fact it is present among very different civilisations (Murphy 1976) such as people of Kosrae in Micronesia (Waldo 1999), Australian aborigines (Mowry, Lennon and De Felice 1994), Bantu (Riley *et al.* 1996), etc. and it is "ubiquitous, appear(s) with similar incidence in different cultures" (Jablensky *et al.* 1992). Therefore schizophrenia, being clearly a condition impacting very negatively on reproductive chances, is an evolutionarily disadvantageous trait, that should be normally destined to rapid erasing by Evolution. But, as opposed to what expected, it has somehow survived and it is still present. Crow proposed a possible solution for this paradox: the predisposition to psychosis could be "a component of Homo sapiens-specific variation associated with the capacity for language" (Crow 2000). In other terms, being the faculty of language developed quite recently in the natural history of human species (50.000 years ago?), cortical centres where these functions are localised must be rather new, too, and therefore those brain areas can easily run into several kinds of failure. Specifically schizophrenia should be determined mainly by the loss of *indexicality*, which is an ethnomethodology concept and represents the phenomenon whereby each description is related to

the context (understood as a system of references and cross-links) of its production and usually indicates much more than what literally expresses. Lack or deficit of indexicality may result, e.g., in the inability to differentiate thoughts from voices (both one's own voice and other ones' voices), i.e. substantially Schneider's first rank symptoms. Results were widely replicated (see e.g. Angrilli et al., 2009).

The presence of altered hemispheric dominance in schizophrenia has been widely documented.

A classic meta-analysis by Iris Sommer (Sommer *et al.* 2001) which authoritatively confirms abnormalities of hemispheric lateralisation in schizophrenic patients compared to healthy subjects. She based on: studies on manual dominance (increased prevalence of left-handedness), studies on dichotic listening (vide infra) (reduction of the normal perceptual advantage of the right ear) and studies on the anatomical asymmetry (reduced asymmetry of the planum temporale).

Functional studies have been more numerous: recent works with fMRI seems to confirm an altered language-related cerebral activation. For brevity only one study is cited (Alary *et al.* 2013); in this paper the cerebral activation of the two hemispheres is recorded during the performance of a linguistic task by observing a reduced left lateralisation in the sample of schizophrenic patients compared to controls.

In addition to Schizophrenia, anomalies of brain asymmetry were associated with a certain number of other psychiatric diseases, such as Major Depressive Disorders (e.g. Bruder et al., 1997), Schizoaffective Disorders (e.g. Wexler et al., 1991), Obsessive-

Compulsive Disorder (e.g. Peng et al., 2015), Panic Disorder (e.g. de Carvalho et al., 2013), Borderline Personality Disorder (de Araujo Filho *et al.* 2014), Schizotypal Personality Disorder (Lindell 2014; Park and Waldie 2016), etc..

Finally a big number of papers on altered lateralisation and BP (I or II, with or without psychotic features) have been written, too (Reite *et al.* 1999, 2009; Caligiuri *et al.* 2004; Royer *et al.* 2015; Ho *et al.* 2017).

AIM OF THE STUDY

The primary purpose of this research is to analyse through fMRI the functional connectivity of a group of patients affected by BD compared to a group of healthy controls, as this kind of studies is still rare in literature.

The secondary aim is verifying the possible application to bipolar spectrum – through the *continuum* theory – of the psychosis paradigm as a hemispheric lateralisation deficit of linguistic functions formulated by T.J. Crow.

MATERIALS AND METHODS

Magnetic Resonance Imaging

§Generic notes of Nuclear Magnetic Resonance.

The (Nuclear) Magnetic Resonance Imaging (MRI) is based on the principle* – discovered after the end of the Second World War, in 1946 – by the Swiss physicist Felix Bloch and his US colleague Edward Mills Purcell (both Nobel Prize for Physics in 1952).

After scanning, the real image is composed of a set of frequencies ν with different spatial orientations, this – by means of a mathematical function called *Fourier*† *transform* – is reduced to a spatial frequency matrix also called *k space* (Twieg 1983) that is very useful for comparing images obtained with different techniques.

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* The centre is a quantum property of subatomic particles such as protons called spin. (Atoms with odd atomic masses – such as protium or ^1H – have what can be defined as a spin net and therefore a magnetic moment.) When spins are in contact with an external magnetic field (B_0) they start a precessional motion around the direction of B_0. The absorption of energy due to the oscillation of B_0 occurs when it assumes the so-called Larmor frequency: $\nu_L=(-\gamma B_0)^{-1}$, where γ is the *gyromagnetic ratio* (or *Landé g-factor*), that is the ratio between angular and magnetic moment. The net magnetization vector has two components: one longitudinal, perpendicular to B_0, and one transverse, parallel to B_0: the return to the original state in the first case takes the name of *T1* (or *spin-lattice*) relaxation, in the second T2 (or *spin-spin*) relaxation.

† Fourier transform of the real function u can be written as:

$$\Im\{u\}(\omega) = \hat{u}(\omega) := \frac{1}{\sqrt{2\pi}} \int_R e^{-i\omega t} u(t)dt \qquad \text{for } \forall \omega \in R$$

Two parameters are basic:

- *TR (time of repetition)*: expressing the time between the various perpendicular stresses;
- *TE (time of echo)*: expressing the time between a perpendicular stress and signal detection.

The operator, by appropriately changing TR and TE, may study (see footnote below):

- *longitudinal relaxation time (T1)*: depends on the interaction between the protons and the surrounding molecules (appropriate parameters: short TR and TE);
- *transverse relaxation time (T2)*: describes the heterogeneity of the internal magnetic fields of the different tissues (appropriate parameters: long TR and TE);
- *proton density*: expresses the different amounts of hydrogen (^{1}H) nuclei (or other elements) resonant and present in the volume unit (suitable parameters: long TR and short TE).

Using MRI scanners, apart from direct structural images, many other techniques can be adopted to obtain particular information, such as FLAIR, DTI, DWI, spectroscopic MRI, multinuclear (different from ^{1}H) MRI, etc.

The one used for this thesis is the *functional MRI* ***(fMRI)***, that provides fast and periodic scans (usually a *«volume»* every 2 or 3 seconds) at low resolution.

Typically, fMRI use the so-called BOLD (Blood-Oxigenation-Level Dependent) effect (Bandettini *et al.* 1992; Turner 1997), discovered by the Japanese applies physicist Seiji Ogawa and his US colleague Kenneth Kwong. In activated brain regions there is an increased consumption of oxygen and glucose by the neuronal pools, as well as the hyperconcentration of some neurotransmitters and an increased blood flow (Kamba, Sung and Ogawa 2007). So there is a change in the relative concentration of oxyhemoglobin and deoxyhemoglobin and this fact is detectable by MRI, especially using T2-wighted sequences (Thulborn *et al.* 1982).

Prior to the positive BOLD signal there is also a weakly negative (probably a result of local neuronal metabolism) which is only evidenced by machines capable of generating an area equal to or greater than 3 Tesla, however fMRI is not recommended for scanners with power less than 1.5 T.

§Brain intrinsic activity.

It has been clarified that most brain activity is not *evoked* (by external stimuli or *free will*[*]) but it is constitutive and by default (Biswal 2012). Just for citing some elements: though brain represents only the 2% of human body mass its metabolic consumption is about 20% (Clarke and Sokoloff 1999) and the further need for energy associated with *extrinsic activation* is very small, usually less than 5% of the baseline level (Raichle and Mintun 2006). Obviously brain intrinsic activity is normally explored in resting

[*] In this paper the central debate of philosophy of mind (monism vs. dualism, determinism vs. free will) has been intentionally left out.

state condition in order to avoid external influences; though other techniques are used (such as EEG, MEG, PET or NIRS and other optical methods) the most adopted neuroimaging system is surely *rsfMRI* (resting state fMRI).

The evolutionary meaning of cerebral intrinsic activity – i.e. "what is the advantage of a so high «basal» activity of brain neurons?" – has been discussed since its very first appearance (Berger 1929; Mink, Blumenschine and Adams 1981) but, precisely due to the complexity of this debate, it cannot be treated in this paper, but just outlined. Apart from the energy expense represented by *spike-generated* glutamate cycling (up to 60-80% of the whole brain), sub-threshold depolarisations (Raichle and Mintun 2006) and basal consumption of cells like astrocytes or inhibiting neurons; the reasons of the huge cerebral resting state activity may be divided into four big groups: the *sensorium* issue (i.e. the fact that most probes need continuously energy to perform continuous detection), the problem of continuity and coherence in time and space perception, *conscience*, and, finally, the organisation of brain networks* (Raichle 2015).

It is important to notice that **networks** detectable in subjects at rest are fundamentally the same shown during a certain task, but with the basic difference that some of them are enhanced and some of them are silenced, wholly or partially (Rosazza and Minati 2011). Number (and features) of brain networks is still highly debated, at the moment it varies from 7 up to ~20 circuitries (Yeo *et al.* 2011),

* The fourth hint might be certainly seen as a generalisation of the second and the third.

but undoubtedly the most widely studied is the Default Mode Network (DMN)*.

Functional Connectivity (FC) of the brain is operational (Friston 1996) and basically stochastic: "temporal correlations between spatially remote neurophysiological events" (Friston *et al.* 1993). FC study by nuclear magnetic resonance is strictly linked to resting-state fMRI (rs-fMRI) (Biswal 2012) and several different networks have been isolated during the last two decades (Biswal, Van Kylen and Hyde 1997; Damoiseaux *et al.* 2006; Lee *et al.* 2012).

The Experiment

§Participants

Patients were selected from those ones followed by the public healthcare system of Padua, Veneto, Italy; healthy controls were recruited between volunteers coming from the same region, mainly in-law relatives or friends (with no genetic links) of patients' who attended a nine-lessons course of psychoeducation on Bipolar Disorders at the Mood Disorder Unit of Padua University Hospital.

The study has been approved by the Ethics Committee of Padua University Hospital and adheres to the principles of the Declaration

* It has several, basic and different functions groupable into three main blocks: the *Self* (autobiographic data, self-reference, consciousness of our own emotions), the *others* (theory of mind, empathy, identification in someone else…) and remembering the *past* + thinking about the *future* (mnemonic retrieval, planning, plot comprehension…).

of Helsinki. All participants provided informed written consent before study entry.

Inclusion criteria for Patient group were: having received a diagnosis of Bipolar (type I or II) for at least one year and being an active outpatient. Specific exclusion criteria were: major psychiatric comordibity, not being in euthymic state at the moment of performing the experiment. Exclusion criteria for Control group were: blood relationship with some members of Patient group, any lifetime psychiatric diagnosed disease, use of psychotropic drugs. Exclusion criteria for all groups were: presence of metal bodies in the skull (or other hindrances to MRI scan), epilepsy and other major neurologic brain comorbidities, left-handedness.

The cohort was composed of 18 patients* affected by BD Type I or II and 16 healthy individuals matched for sex, age and education level.

As similar studies (FC analysis of BD with tasks stimulating different hemispheres) do not exist in literature, yet, a prior power statistical analysis was not possible; therefore this study must be considered exploratory. This implies that some features (such as significant differences between groups) were not detected.

§Clinical assessment

* The pool of patients was composed by 19 subjects (10 men and 9 women), but one of them (male) showed an altered structural MRI due to a – previously uncommunicated – traumatic brain injury located at upper-left temporal area that was happened in young age; for this reason he was discarded.

In order to evaluating handedness every subject – regardless of the group – had performed the Edinburgh Handedness Inventory (EHI) (Oldfield 1971), the most widespread test in literature.

Diagnoses of all subjects affected by Bipolar Disorder were revised through specific performing of MINI International Neuropsychiatric Interview (Sheehan *et al.* 1998) and results adapted to fill DSM-IV-TR (APA 2000) criteria.

Comorbidity for personality disorders was excluded administering the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First and Gibbon 2003).

Then all patients underwent to a test battery to assess psychiatric state *(see Table 2)*:

- HAM-D (Hamilton Depression Rating Scale) (Hamilton 1960), in order to evaluate the presence of depressive symptoms;
- YMRS (Young Mania Rating Scale) (Young *et al.* 1978), in order to evaluate the presence of residual manic symptoms;
- ASRM (Altman Self-Rating Mania scale) (Altman *et al.* 1997), in order to get a self-evaluation of hyperthimic symptoms;
- STAI-Y (State-Trait Anxiety Inventory – Form Y) (Spielberger *et al.* 1983), in order to get an assessment of trait and state anxiety;
- PANAS (Positive and Negative Affective Scale) (Watson, Clark and Tellegen 1988), in order to get a quick draft of

subject's (positive and negative) affectivity in the week before the scan.

Psychopharmacologic therapy of patients has also been recorded as well as possible history of psychotic symptoms, age of onset, duration, mood temporal pattern, number of manic, hypomanic or depressive episodes *(see →Table 2)*.

§MRI scan and neuropsychological tasks

Neuroimages were obtained using a Siemens MAGNETOM® 1.5 T MRI system (Siemens Healthcare, Erlangen, Germany) at the Radiology Department of Padua University Hospital; the specific head coil was mounted in order to ameliorate image quality of brain tissues. After having read and signed the informed consent form, all subjects - undressed and checked for ferromagnetic bodies – were helped to lie down on MRI scan mat and finally to wear headphones and glasses*.

For every subject 6 MRI sequences were acquired (in about 45-50 minutes): brief localizer, structural MP RAGE scan (Brant-Zawadzki, Gillan and Nitz 1992), rsfMRI (201 volumes, 8'05"), brief field map (to correct possible motion artefacts), first (phonemic) task fMRI (151 volumes, 6'00"), second (spatial) task fMRI (151 volumes, 6'00") . Additional data on rsfMRI are: voxel 1.796875×1.796875×6.0 mm (≈19.37 mm^3), matrix 64×64×36 voxels, TE 2390 ms, TR 50 ms, flip angle 90°.

* All subjects were asked to wear special headphones and video-glasses (Visuastim®, Resonance Technology Inc., Northridge, CA, USA) in order to be able to undergo two (visual) neuropsychological tasks during acquisition.

The first task was addressed to study phonemic fluency (see e.g. Grogan et al. 2009): using E-Prime® software (Psychology Software Tools, Sharpsburg, PA, USA) three capital letters for two minutes each (specifically "C", "P" and "S") were shown to subjects and they were asked to think every time to all the common thing nouns beginning with that letter. At the end of the acquisition people had to repeat in 30 seconds all thought nouns about the last letter ("S"). Wrong words – such as adjectives, adverbs, verbs, proper nouns, words deriving from each other, etc. – were not taken into account. The aim of this exercise was to elicit linguistic functions and therefore to evoke left hemisphere activity*.

The purpose of the second task was eliciting spatial (vector) functions and so evoking right hemisphere activity. It was about mental rotation: a picture composed by three sections of five figure each (cubes 3D-assembled, see *Fig. 4*) (Shepard and Metzler 1971) were displayed, the first one was the reference for its section and only two of the other four figures represented the reference rotated, while the remaining two represented simply different aggregations of cubes. The purpose of this exercise was eliciting spatial (vector) functions and so evoking right hemisphere activity.

* As some linguistic functions involve also some brain areas located in the right hemisphere, we chose such a phonemic task in order to evoke as more specifically as possible left areas activity, indeed in phonemic processes right hemisphere can be – partially – involved just in particular lexical contexts, even in presence of a left lesion (Wolmetz, Poeppel and Rapp 2011).

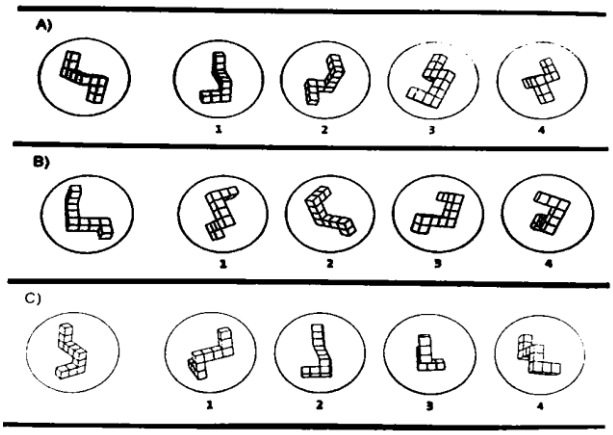

Figure 4. ***Mental rotation task.*** Adapted from *Shepard&Metzler, Science, 1971.*

§Data pre-processing

First of all structural images were examined by an expert neuroradiologist (Renzo Manara, professor of Radiology at the University of Salerno) in order to exclude those subjects presenting macroscopic alterations of the central nervous system.

Common preprocessing of MRI images (both for ICA and Graph Analysis) consisted in: erasing of the first five volumes, reorientation, motion correction, skull-stripping, registration into matrices, mask-building, rescale, smoothing, despiking, application of a high-pass filter (0.005 s) to frequencies and detrending.

For these steps mainly two* different software suites were used: FSL (FMRIB Software Library v5.0, University of Oxford, UK) (Smith *et al.* 2004) and AFNI (Analysis of Functional NeuroImages v17.1.03, NIMH-NIH, Bethesda, MD, USA) (Cox 2012). For despiking

* Only for file conversion (from DICOM to NIfTI) and for the first visualisation a third software has been used: MRIcro (CRNL, University of South Carolina) (Rorden *et al.* 2012).

we used a special algorithm (Patel *et al.* 2014) running under MATLAB environment (Mathworks, Natick, MA, USA).

§Independent Component Analysis

Historically the origin of the Independent Component Analysis (ICA) may be recognised in the need to find a solution for *binaural* phenomena such as the so-called *cocktail party effect* (Cherry 1953) and *dichotic listening*. Even if the most classical examples, which date back to the 1950s, do not concern medical problems (e.g. air traffic controllers), the first mathematical approach was built to be applied to neuronal network activity (Hérault and Ans 1984).

ICA is a computational method for separating a multivariate signal into additive subcomponents; these must be non-Gaussian signals/data and not correlated to each other (i.e. independent).

In the last two or three decades robustly formalised ICA (Comon 1994) has been proved being a powerful and reliable tool to detect sources of electromagnetic brain activity applicable to several functional methodologies in neuroscience, also to fMRI (Calhoun *et al.* 2001; Beckmann 2005; Calhoun and Adali 2012). It proved to be an useful tool both in psychiatric and neurologic conditions (Manara *et al.* 2015).

In particular a specific technique, called Temporal-Concatenation Group ICA (TC-GICA) (Zuo *et al.* 2010), was adopted to extract group-level components from the database using MELODIC software – FSL (FMRIB, Oxford, UK) (Jenkinson *et al.* 2012).

After this step all isolated components were inspected by visual analysis and those recognised as non-artefacts underwent dual-regression approach in order to be standardised into Z-score maps

(Zuo *et al.* 2010), then these ones were used to compare the two groups, with age and gender as confounding variables. Finally spatial maps were analysed using nonparametric permutation tests (Nichols and Holmes 2002) using the Threshold-Free Cluster Enhancement method (TFCE – FSL, FMRIB, Oxford, UK) (Smith and Nichols 2009) and multiple comparison correction (Alonso *et al.* 2015), with $p<0.05$.

§Graph Analysis

Besides ICA, neuroimaging data were also processed with Graph Analysis (GA)*. Graph Theory is a still relatively unusual field of *discrete* Mathematics and traditionally its origin is traced back to Leonard Euler (Basel 1707 – St. Petersburg 1783), who resolved first the so-called *"Seven Bridges of Könisberg" problem*, a logical enigma very popular in the 17th and in the 18th centuries.

In its simplest definition, a *graph* is an ordered pair comprising a set of two *objects* (which can be *vertices*, *nodes* or *points*) and one or more *connections* (and they are *edges*, *arcs* or *lines*); in a more general approach graphs are mathematical structures used to model pairwise relations between objects. Graph Analysis is therefore very suitable for studying almost any kind of network.

Apart from infrastructures, another well-known application of GA was to the famous study of the psychologist Stanley Milgram's (New York 1933 – 1984) on the degree of social separation between two randomly chosen citizens living in different states of the USA.

* For further compatibility between ICA and GA applied to rsfMRI see →(Ribeiro de Paula *et al.* 2017).

The analysis revealed that the average social distance between two individuals is much shorter than what is commonly thought, hence the theory of the *"small world network"*.

The international neuroscientific community has been applying successfully GA to brain functional connectivity in general – and to fMRI in particular, too – for more than a decade (Astolfi *et al.* 2007) and it is considered a robust and reliable method.

In order to apply Graph Theory to the study of functional connectivity, brain networks were built using Network Based Statistic (NBS) (Zalesky, Fornito and Bullmore 2010). Then global connectivity was analysed to detect differences in connectivity between the two groups (patients and controls) under the three conditions: in resting state, while performing the verbal fluency task, and while performing the mental rotation task. Through mixed model analysis, differences between resting state and verbal task were investigated comparing the two groups and then the same condition was examined in the two groups separately. Then, FC differences between the two groups (patients and controls) were detected and analysed using NBS (*vide supra*). Finally, in order to compare FC in resting state and FC during the execution of each task, first between the two groups and then in the two groups separately, repeated measurements were carried out (mixed model analysis).

§Statistical Analysis of neuropsychological data

Behavioral/neuropsychological data of the two tasks acquired during the experiment were analysed using an ANCOVA test covariating age and schooling (threshold t=3.1, 5000 permutations, p<0.05, network-based correction).

RESULTS

§Demographic and clinical data

Whilst all controls accomplished regularly neuropsychological tasks within the scanner, one patient (out of 18) could not carry out all MRI sequences (because of excessive anxiety during image acquisition) and so he was excluded. Therefore all following data are referred to a Case group of 17 patients.

Personal and anamnestic data of the two groups are summarised in *Tab. 1* while psychiatric tests scores (patient group) are shown on *Tab. 2*.

	Patients (*n*=18)	**Controls** (*n*=16)
Age (years)	54.00±11.52	51.18±11.43
Gender (M:#, F:#)	M:9, F:9	M:8, F:8
Education (years)	12.24±4.25	16.00±4.42
Handedness	Right (18/18)	Right (16/16)
Diagnosis (BD1:#, BD2:#)	BD1:9, BD2:9	-
Age at of onset (years)	31.75±15.97	-
Duration of disease (years)	21.58±10.65	-
W/ psychotic symptoms (#)	9 (50.00%)	-
Manic episodes[1] *(#)*	0.91±0.94	-
Hypomanic episodes[1] (#)	1.63±1.85	-
Depressive episodes[1] (#)	3.45±2.42	-
Psychiatry admissions[1] (#)	1.36±1.96	-
Remission (years)	4.37±4.44	-

Notes: [1] Lifetime.

Table1. ***Personal, anamnestic and handedness data*** *of the two groups.*

HAM-D	5.81±4.00
YMRS	2.19±2.83
ASRM	5.25±4.71
PANAS-P[2]	28.53±8.25
PANAS-N[2]	20.40±7.40
STAI-Y1	38.62±10.82
STAI-Y2	48.00±8.44

Notes: [2] PANAS-P and PANAS-N are referred to positive and negative score respectively.

Table 2. ***Clinical tests scores*** *(Patient group only)***.**

As shown in *Tab. 1*, all subjects were right-handed (regardless of the group belonging), EHI average score was 92.50(±10.15)%. Finally, there was a significant difference between the two groups for the variable *schooling* (for $p<0.05$).

All patients were psychopharmacologically treated. Used drugs were[*]:

- Mood stabilisers (14): 4 carbolithium, 10 antiepileptics (7 valproate, 2 lamotrigine, 1 gabapentin);
- Atypical antipsychotics (16): (10 quetiapine, 4 asenapine, 2 aripiprazole);

[*] Digits are referred to the number of patients taking that drug.

- Antidepressants (10): 5 SNRIs* (4 venlafaxine, 1 duloxetine), 3 SSRIs † (1 escitalopram, 1 fluvoxamine, 1 sertraline), 2 NaSSAs‡ (2 mirtazapine);
- Anxiolytics: 1 benzodiazepine (1 diazepam).

§Neuropsychological (tasks) data

Scores at the first task (verbal fluency) did not displayed significant differences between groups. Having set significance level for p=0.05, accounted variables were: number of words having a different root *(Flu)* (p=0.54), number of words having the same root *(Flu+)* (p=0.40), number of repetitions *(FluRep)* (p=0.57), number of intrusions *(FluIntr)* (p=1.00). (See *Fig. 5.*)

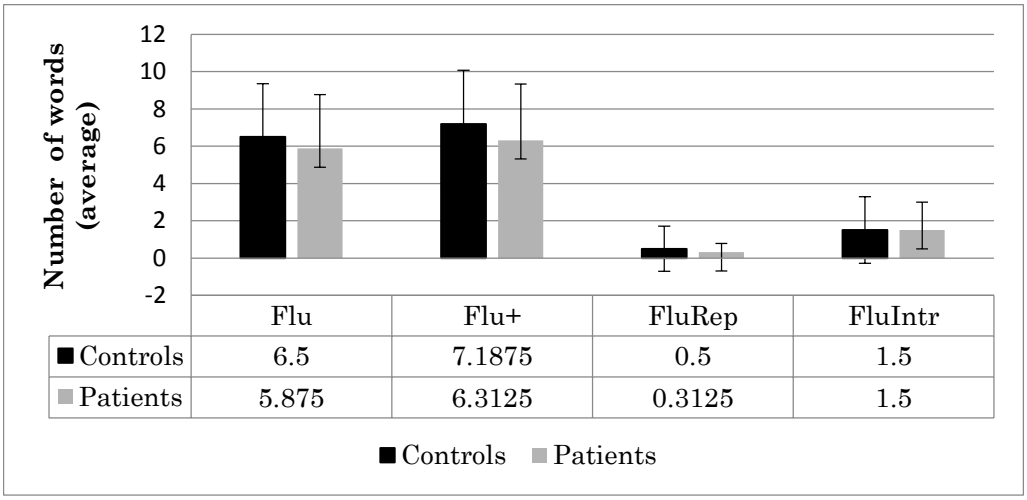

Figure 5. ***Verbal Fluency task score.***

* Serotonin–Norepinephrine Reuptake Inhibitors.

† Selective Serotonin Reuptake Inhibitors.

‡ Noradrenergic and Specific Serotonergic Antidepressants.

Results of the second task (mental rotation) showed a significantly (p=0.04) higher accuracy in answering by Control group

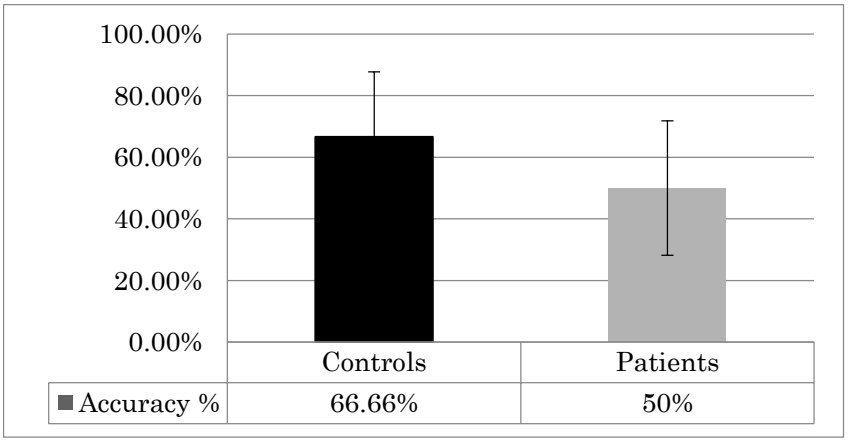

Figure 6. ***Mental Rotations task score.***

(66.67±21.08%) compared to Patient group (50.00±21.85%). (See *Fig. 6.*)

§MRI Data (and correlations)

ICA of rsfMRI individuated 30 required independent components; after eye-evaluation just 11 of them were judged non-artefacts. They are: default mode network (DMN), auditory network, dorsal attention network (DAN), ventral attention network (VAN), (3) visual networks, executive control component, frontal (inferior) networks, frontostriatal circuit, parietal networks.

Adopted software (MELODIC) performed automatically dual regression to investigate group differences. Comparing patients' and

Area	**Network**	**BA**	**Brain Region**	**MNI coordinates (Peak)** (mm)			**Cluster** (voxel)
#1	Auditory	19	Cuneus	3	-87	36	4
#2	Auditory	22	STG	-57	12	-3	1
#3	DAN	7	Precuneus	-12	-57	63	145
#4	DAN	40	IPC	33	-42	39	64

Table 3. ***ICA comparison.*** Areas significantly (p=0.05) less connected in patients compared to controls.

controls' components three main significant areas (for p=0.05) within networks were found less connected shown in *Tab. 3*.

In order to control possible type I errors in multiple comparisons, we performed a False Discorvery Rate (FDR) correction (Benjamini and Hochberg 1990) which can be expressed by the following equation:

$$p_c = \frac{\alpha(m+1)}{2m}$$

where p_c is the *corrected* p, α is the previous p (0.05) and m is the number of hypotheses tested (11): therefore $p_c \approx 0.027$.

Applying the new cut-off only two comparison survived, both in DAN, but only one with a considerable number or significant voxels (64≈1.24 cm^3), as it is showed in *Tab. 4* and *Fig. 5*.

Area	**Network**	**BA**	**Brain Region**	**MNI coordinates (Peak)** (mm)			**Cluster** (voxel)
#3	DAN	7	Precuneus	-12	-57	63	64
#4	DAN	40	IPC	33	-42	39	1

Table 4. ***ICA comparison (corrected).*** Areas significantly (p=0.027) less connected in patients compared to controls (corrected for multiple comparisons). [Also the centre of gravity of Area #3 (x=-12.7, y=-59, z=54.8) results to be located in BA 7; Area #4 is formed by only one voxel.]

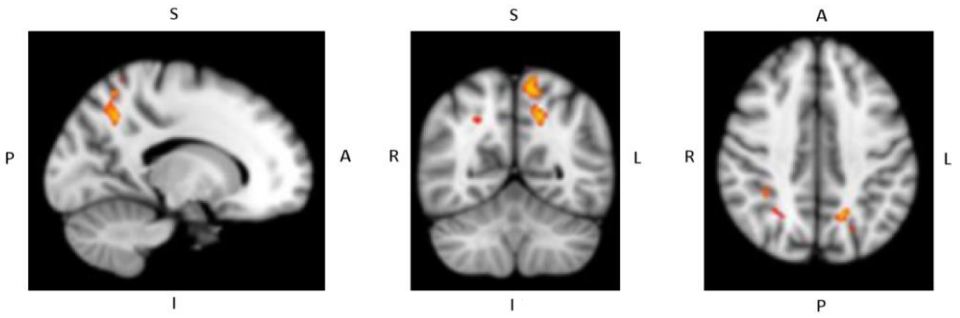

Figure 7. ***Network comparison.*** This picture highlights in the three orthogonal projections (sagittal, coronal and axial) those areas in DAN significantly less connected in patients compared to controls. No other networks showed significant areas (after FDR correction). [Legend: red>orange>yellow].
Please notice that, observing the picture at left (sagittal) we can understand that the two big spots in the left hemisphere we can see in the middle picture (coronal) represents in reality only one volume.

Both networks (DAN and auditory) suspected of being less connected in cases than in controls (see →*Tab. 3*) were compared to task performance. Whilst DAN showed no correlation with task score, (basically weaker) patients' auditory network functional connectivity seemed correlated with (poorer) performance at mental rotation task, but it is important to underline that – after FDR correction – auditory network FC difference between groups is not significant any more (for further information, see *Supplemental Materials*).

Graph Analysis revealed no significant difference between the two groups in global analyses; the following parameters were taken into account:

- *global efficiency*, no detected differences;
- *assortativity*, non-significantly increased in Patient group;
- *clustering coefficient*, non-significantly and weakly increased in Patient group;
- *local efficiency*, non-significantly and weakly increased in Patient group;
- *modularity*, nearly significantly ($p<0.08$) increased in Patient group;
- *centrality indices*: the *mean node betweenness* and the *mean edge betweenness* showed a weak significance (P>C).

[For graphics, see →Supplemental Materials.]

Differences in connectivity between the two groups were evaluated using NBS analysis and ANCOVA (covarying age and school). Whilst in resting state there is no significant difference, during the verbal fluency task Patient group exhibited lower connectivity than the control group with a (weakly) statistically significant difference (p=0.049) (see *Fig. 8*).

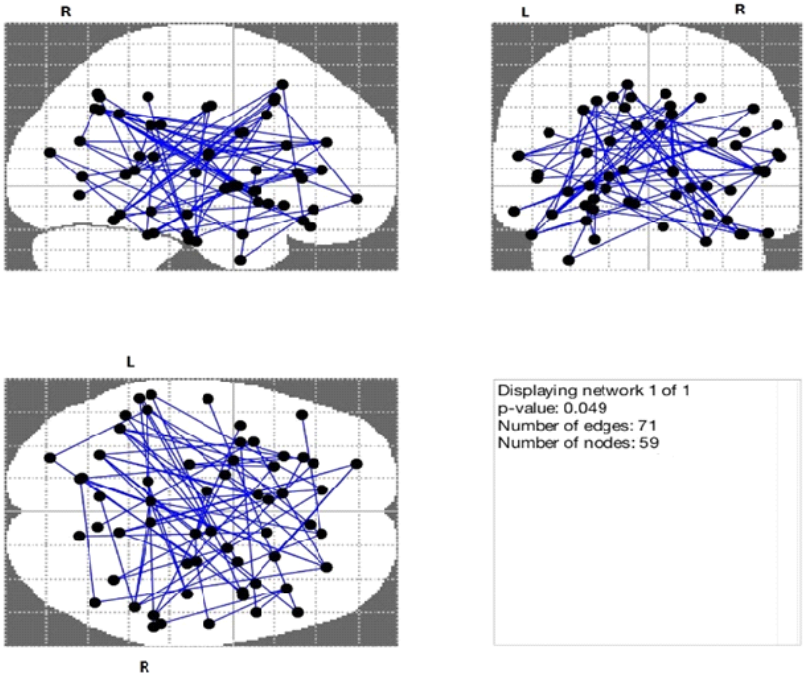

Figure 8. ***Functional Connectivity (GA) in verbal fluency task*** *(Patient group vs. Control group, weaker connections).* The figure shows a significantly lower connectivity in the bipolar patient group than the healthy control group. Objects/connections consist in 59 nodes and 71 edges. *(Image obtained by FSL.)*

Then, by analyzing hemispheric asymmetries in the (significantly lower) FC emerging in patients, it has been shown a decreased connectivity between inter-hemispheric areas and, among intra-hemispheric connections, the lowest FC was found at left. *(For tables and graphics, see Tab. 5 and Fig. 9.)*

Left intra-hemispheric	18
Inter-hemispheric	42
Right intra-hemispheric	12

Table 5. ***Verbal Fluency Task.*** *Number of connections significantly functionally inferior in patients compared to controls.*

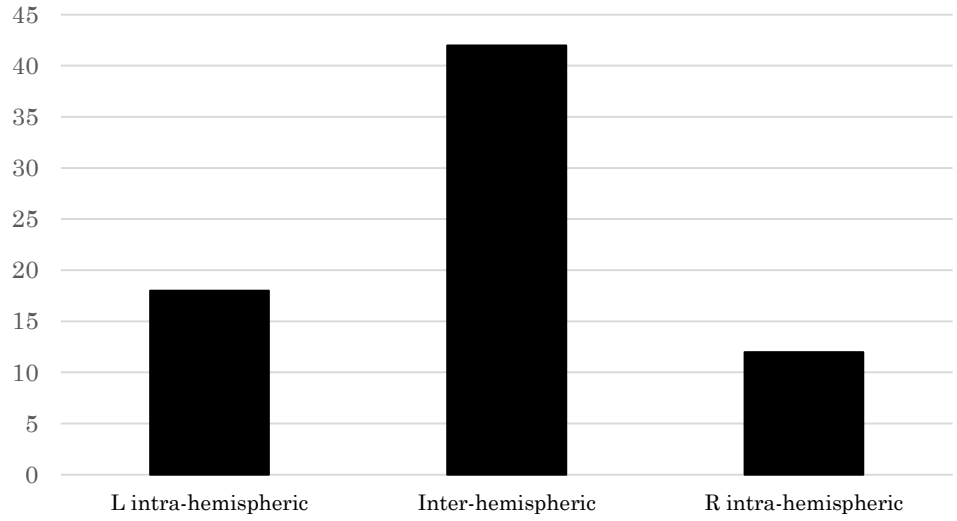

Figure 9. ***Verbal Fluency Task.*** *In ordinates: number of connections significantly functionally inferior in patients compared to controls.* There is a decreased inter-hemispherical bipolar connectivity and, to a lesser extent, left intra-hemispherical connectivity, too.

The relationship between FC and task performance has been evaluated using ANCOVA test. No significant correlation between performance at the phonemic task and connectivity (both in resting state and during the verbal fluency test), and no significant differences between the two groups emerged.

Than a new analysis has been performed: as neural *firing* can be considered a sort of *«over-basal» activation* (about +5%) *(see →"Brain intrinsic activity" paragraph)*, we considered this new data (the difference between the number of connections active during task performance and while resting, via mixed model analysis) comparing cases and controls. This comparison (relative to the previous one)

showed a decreased number of significant inter-hemispheric and right intra-hemispheric connections (patients vs. healthy subjects), while left intra-hemispheric ones remained the same, as you may see from *Tab. 6*.

Left intra-hemispheric	18
Inter-hemispheric	20
Right intra-hemispheric	7

Table 6. ***Verbal Fluency Task vs. Resting State.*** *Number of connections significantly functionally inferior in patients compared to controls.*

This describes a highly asymmetric condition where there is a ***left lateralisation deficit*** while eliciting language faculties in people affected by BDs is glaring, as you may clearly see from *Fig. 10*.

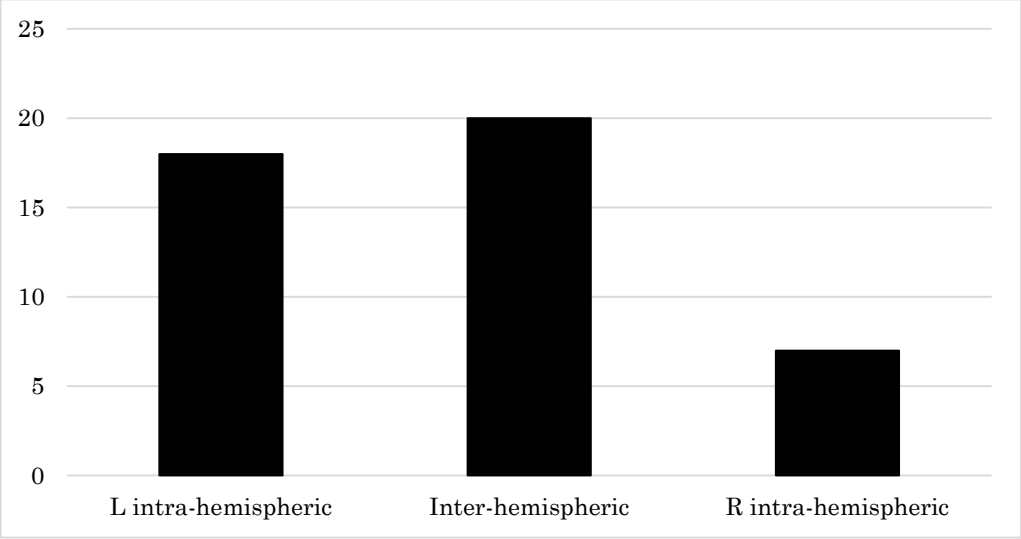

Figure 10. ***Verbal Fluency Task vs. Resting State.*** *In ordinates: number of connections significantly functionally inferior in patients compared to controls*. There is a decreased inter-hemispherical and left intra-hemispherical connectivity among bipolars.

There was no significant difference in FC between the resting state and the verbal task in Patient group. Among controls on the contrary the difference between resting state FC and verbal task FC

in the Control group was significant: connectivity during the verbal task increased more between inter-hemispheric areas (#145) than that of intra-hemispheric areas of both right (#64) and left hemisphere (#68).

[For the complete list of connections, see →Supplemental Materials.]

DISCUSSION

Comments to data

§Networks and Attention (ICA)

Since the early 2000s two different networks have been identified for attention controlling (Corbetta and Shulman 2002) nowadays sturdily recognised as Dorsal Attention Network (DAN) and Ventral Attention Network (VAN) (Vossel, Geng and Fink 2014). The first one (DAN) – which is normally almost symmetric – is responsible of the "goal-directed" screening of stimuli and reactions; it underlies a *top-down* process driving data flow from «higher» to «lower» brain centres transmitting information that is not principally coming from the sensorium (*immediate* external world perceptions) but rather from memory retrieval of old experiences (and their elaboration). The second (VAN) is highly lateralised to the right hemisphere and provides the "stimulus-driven" attention by a *bottom-up* process from *immediate* perceptive inputs, via sensorial analysis, directly to motor reaction (Kucyi *et al.* 2012).

Functional neuroanatomy of DAN was described (Szczepanski *et al.* 2013) as well its hierarchic relationship with the other main networks (Lee *et al.* 2012).

DAN has been studied in physiologic conditions showing capability of predict specific characteristics – such as attention level in children (Rohr *et al.* 2016) – and to be predictable by specific characteristics – such as eye movements during auditory attention

task (Braga *et al.* 2016), but also in pathologic cases. DAN alterations are associated with hallucinations not only in psychiatric disorders, but also in neurologic ones such as Parkinson's disease (Shine *et al.* 2014). Then DAN anomalies were found particularly in Schizophrenia(Gaebler *et al.* 2015; Jimenez *et al.* 2016), other major psychoses with/without recreational drug abuse (Ipser *et al.* 2016), Depression (Sambataro *et al.* 2017), Attention Deficit Hyperactivity Disorder (ADHD) (Son *et al.* 2017) and in BD (Brady *et al.* 2017; Son *et al.* 2017). Among psychotic those alterations proved to be at least partially correctable by dopamine antagonists such as risperidone (Kraguljac *et al.* 2016).

Furthermore has been recently confirmed (Esposito *et al.* 2017) that DAN and Default Mode Network (DMN) anticorrelates, moreover – in agreement with Fox&Raichle's original theory (Fox *et al.* 2005) – DAN would be the core of the so-called *task-positive network* opposed to a *task-negative network* of which DMN is part (and this dynamic equilibrium would dominate the whole normal brain activity). Curiously, in the latest quoted paper, the authors found as first peak foci for intrinsically defined anticorrelated networks the same Brodmann areas (7 and 40) shown in *Tab. 3* (see Table 1, p.9676 in Fox et al., 2005).

Asymmetry. In a very recent article finding alterations of DAN in BD the strongest FC difference found between patients and controls (*see* Fig. 3 *in* Son et al., 2017) was the hyperconnectivity of right (but not left) Inferior Frontal Gyrus (IFG) with Thalamus and Temporo-Parietal Junction (TPJ). Both IFG and TPJ are basic components of DAN, TPJ is maybe the most asymmetric one, being the right one (rTPJ) found more active than the left one compared to

healthy subjects; rTPJ has been found particularly involved in social cognition (Decety and Lamm 2007).

In the present work ICA comparison allowed us to highlight two zones within DAN which are significantly (p=0.027) less functionally connected in patients compared to controls, but after FDR correction the previously called Area#3 constitutes (being 64 voxels vs. 1*) more than 98% of significant volume (~1.7 cm^3, being «new» voxels 3mm×3mm×3mm). These voxels correspond – within Brodmann Area 7 (BA 7) – approximately to part of *left* Superior Parietal Lobule (lSPL); particularly its peak is located in Precuneus (lPC).

The function of SPL within DAN seems to be double (Szczepanski *et al.* 2013): its connection with supplementary eye fields (in frontal lobe) should be basically responsible of spatial attention (both in viewer- or object-centred coordinates), then it is transiently activated during voluntary shifts of attention.

§Whole brain and hemispheric activity (GA)

The good performance of patients' at the Verbal Fluency task seems to have a *graph* equivalent in the preserved *global efficiency* (no detected differences vs. controls). Even if not significantly *clustering coefficient*, *local efficiency* and above all *modularity* in subjects affected by BDs tended to be increased compares do cases. This parameter is important because it estimates the size of the network consisting of modules in which many arches connect nodes, while few arches connect nodes between different modules. This kind

* In this text Area #4 is not taken into account because – even if using FSL even very small volumes should be considered – 1 single voxel is really not very meaningful.

of agglomeration of nodes assumes a precise functional sense, as it allows the formation of coherent areas in the brain, that is, with a precise function. Furthermore *betweenness* – a centrality index – is increased (P>C).

Asymmetry. *Over-basal* firing showed a clear lateralisation deficit in patients compared with controls during the phonemic task, as you may see from *Fig. 9*.

§Limits

The main limits of this experiment are two:

- the small numerosity of sample, which probably hindered the significance of certain variables (e.g. modularity);
- the matching for schooling between patients and controls (a posteriori) is not precisely balanced (in favour of controls group). This can be a responsible factor for their poorer performance at Visuo-Spatial task (less trained);
- the use of a 1.5 T field instead of a 3.0 T scanner (which is commonly considered probably the gold standard for fMRI acquisition) limited the quality and the definition of neuroimaging data;
- the relative heterogeneity of the inclusion diagnosis: Bipolar Disorder. If the numerosity of the sample had been bigger, the presence of both types (I and II) could have possibly revealed a gradient in alterations (e.g. left lateralisation deficit) where the presence of manic episodes (and psychotic symptoms) would have been

associated to a framework more similar to schizophrenia – for this reason .

§Conclusions

As previously stated, mental rotation task was originally chosen because of its power to activate preferentially right cortex, but in reality visuospatial attention system is absolutely the most studied in the literature and usually used as a paradigm for other attention systems (Vossel, Geng and Fink 2014). Moreover DAN and VAN are probably *supramodal attention systems* (Macaluso 2010), not directly depending by any specific sensory source/way. An imperfect matching for education and the lack of a complete IQ evaluation for all subjects may anyway reduce the significance of the quantitative implications of this item.

A recent study reporting an eventual increased FC of BD patients' attention networks only in VAN (Son *et al.* 2017). In one case DAN has been found altered in BD patients (both in euthymic and manic phase), but strangely increased compared to controls (Brady *et al.* 2017), DMN on the contrary was found hypoconnected (above all in left-frontal regions). However – thinking e.g. about expanded mood phases – it is instinctively logical to consider that *self-inducible* (goal-oriented) attention (DAN) should be more affected than *externally controlled* (stimulus-driven) attention (VAN) in BD: this would simply explain *distractibility*, which is a typical symptom during mania or hypomania.

Very interestingly some authors (Hahn *et al.* 2016) found in schizophrenic patients a substantially normal functioning of DAN during visuo-spatial attention task, but at the same time they described an increased activity of DMN. Data recollected for this article show the contrary a decreased connectivity in a particular region (lPC) of DAN in bipolar subjects during resting-state, while no significant DMN alterations are shown. A possible explanation for this apparent contradiction can be that DAN is affected both in Schizophrenia and BD, but in Schizophrenia DAN loses its power to down-regulate DMN, that therefore is found overexpressed. This hypothesis is in line with the above mentioned *continuum theory*.

DMN and DAN were found simultaneously altered in other psychiatric disorder (e.g. ADHD), but the reciprocal anti-correlation seems respected (McCarthy *et al.* 2013). Therefore it is important to state that we do not have at the moment any strong element to assert that in BD the mutual control between DMN and DAN is compromised. Indeed a limit of this study is the numerosity that does not allow us to exclude the possibility of minor (sub-threshold) changings in DMN FC, furthermore a very recent study showed how much this correlation may vary even within the same subject (Dixon *et al.* 2017).

DMN is clearly interesting for mood and psychotic disorders and was found altered in Schizophrenia (Meda *et al.* 2014), BD (Öngür *et al.* 2010) and depression (Posner *et al.* 2016). For some authors (Utevsky, Smith and Huettel 2014) Precuneus is the *functional core* of DMN, being – among other things – a *distinct hub* showing task-dependent (decision-making) connectivity with DAN and left Fronto-Parietal Network (lFPN). FPN is another control/attention network (probably for planning and emulating) (Gerlach *et al.* 2014; Ptak, Schnider and Fellrath 2017) possibly central in psychiatric symptom

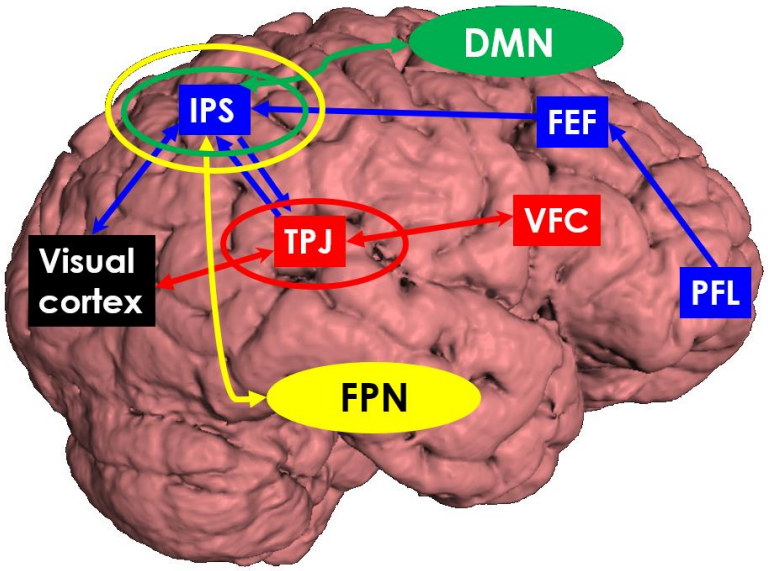

Figure 11. ***Integration of attention networks.*** *In red VAN and in blue DAN.* The integration between the two attention networks each other and with the Default Mode Network and the Fronto-Parietal Network could be crucial. Most asymmetry is basically given by VAN.
Picture drawn by the candidate.

perception (Cole, Repovš and Anticevic 2014) (see *Fig. 11*).

It is possible in our opinion that SPL (and particularly left Precuneus) is the main node where *task-positive system* (DAN, FPN…) and *task-negative system* (DMN…) regulate each other.

Patients showed a decreased functional connectivity lateralisation but this (unlike Schizophrenia) did not affect verbal fluency and is not significantly present on resting state data.

Besides cases displayed a higher hemispherical segregation compared to controls, they also showed similar global efficiency scores, probably thanks to a good integrative function which can preserve the economic (cost-effectiveness).

Pathologic network alteration described in this paper is therefore asymmetric: BD patients' deficit of FC is clearly lateralised at left (probably linked with language – GA – and voluntary attention shifting – ICA); this is fully in agreement with Timothy John Crow's theory.

Nevertheless other theories can explain this phenomenon. A good example can be paid if we accepted – or considered acceptable – a phenomenological and psychoanalytical concept (relatively still widespread above all in the past) that manic and hypomanic phases are at least partly determined by reaction to *negative affect* (or counter-push from depressive state). In that case Davidson's (Davidson 1998) and Allen's (Allen *et al.* 2004) studies would give an alternative explanation: they argued that the location of negative affect is the right hemisphere. Furthermore "frontal EEG asymmetry" would "serve as both a moderator and a mediator of emotion- and motivation-related constructs" (Coan and Allen 2004). From this point of view a relative right asymmetry (shown by weaker left intra-hemispheric and inter-hemispheric connections) could

characterise subjects affected by BD in euthymic phase as a trait mark*.

§Perspectives

The first and most obvious extension of this investigation should be to increase of numerosity.

A much bigger sample of subjects would also allow researchers to get a representative population stratified by severity of symptoms through diagnoses (e.g. BD2 < BD1 without psychotic symptoms < BD1 with psychotic symptoms < Schizoaffective Disorder–Bipolar Type) for better studying the *continuum*. A wide sample is desirable not only because neuroradiological alterations can be subtle, but also because sex differences may be big (and interesting to investigate) and neuropsychological features distributed non-linearly along the *continuum*.

This experience is part of a wider range of researches to investigate the aspects of hemispheric lateralisation in the psychopathologies of (the old) Axis I. After EEG (ERP) application to BDs and MDD, it would be interesting:

- study of cerebral asymmetries in patients by means of *pre-impulse inhibition (PPI)* – startling phenomenon – by bilateral electromyography of both orbital muscles;
- study of the anatomical alterations of physiological asymmetry by high definition MRI (7 T) of other candidate

* In another work (not published yet, *see section "Perspectives"*) increased EEG ß activity in the right Middle Frontal Gyrus in subjects affected by Major Depressive Disorder compare to healthy controls.

brain structures (such as lateral ventricles or *indusium griseum*)

- combination of neuroimaging and genetic techniques above all to analyse of PCDH11X/Y on lateralisation (ventricles, mini-columns, etc).

BIBLIOGRAPHY*

Explanatory Notes

For this paper, the OUP (Oxford University Press *SciMed*, author-date) standard for bibliographic indexing has been adopted. Only for the first historical introduction (the sub-chapter "BIPOLAR DISORDER: A BRIEF HISTORY") references have been put on footnotes as from European humanistic tradition.

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ROUGH SUPPLEMENTAL MATERIAL

List of candidate genes for Bipolar Disorders (and psychoses) (Kato 2007).

Gene name	Chromosomal region	Function/note	Rationale: Association with schizophrenia	Rationale: Linkage	Ref.
Positive studies					
PERIOD3	1p36.23	Circadian rhythm	–	–	3
RGS4	1q23.3	Regulator of G-Protein Signaling 4	+	–	4,5
DISC1	1q42.1	Cloned from translocation break point	+	+	6
IL-1 cluster	2q13	Immune system	+	–	7
SST	3q28	Somatostatin	–	–	71
WFS1	4p16.1	Wolfram syndrome 1	–	+	9
PDLIM5	4q22	Adaptor protein (PKC/Ca^{2+} Channel)	+	+	10
FAT	4q35	Cadherin	–	+	11
DRD1	5q35.1	Dopamine D1 receptor	–	+	12,13
GRM4	6p21.3	Metabotropic glutamate receptor 4	+	–	5
GRM3	7q21.1-q21.2	Metabotropic glutamate receptor 3	+	+	5
NRG1	8p21-p12	Neuregulin 1	+	+	14
HSPA5	9q34	Endoplasmic reticulum chaperone	–	+	15
ARNTL(BmaL1)	11p15	Circadian rhythm	–	+	3,16
NCAM1	11q23.1	Cell adhesion molecule, neural, 1	+	+	17
HTR3B	11q23.1	Serotonin 3B receptor	–	+	18
GRIN2B	12p12	*N*-Methyl-D-aspartate receptor subunit 2B	+	–	5
TIMELESS	12q12-q13	Circadian rhythm	–	–	16
CUX2	12q23-q24	Regulator of NCAM expression	–	+	19
FLJ32356	12q23-q24	Unknown	–	+	19
DAO	12q24	D-Amino acid oxydase	+	+	5,20
Citron	12q24	Serine/threonine protein kinase 21	–	+	21
G72 (DAOA)	13q34	D-Amino acid oxydase activator	+	+	22–25
GCHI	14q22-24	GTP cyclohydrolase I	–	+	26
GABRA5	15q11-q13	GABA-A receptor alpha 5 Subunit	–	–	27
SLC12A6	15q13-q15	KCC3; potassium chloride co-transporter	+	–	28
NAPG	18p11	SNAP (Soluble *N*-ethylmaleimide-sensitive fusion (NSF)-attachment proteins)	–	+	29
CHMP1.5	18p11.2	Unknown	–	+	30
PIK3C3	18q12.3	Phosphatydilinositol kinase 3C3	–	+	31
AD4D2	18q21.1	A gene with triplet repeat	–	+	32
TRPM2	21q22.3	Store operated Ca^{2+} channel	–	+	33
BCR	22q11	Breakpoint cluster region	–	+	34
MLC1	22q13	WKL1, cation channel	+	+	35
SYNGR1	22q13.1	Synaptogyrin 1	+	+	36
GPR50	Xq28	G protein-coupled receptor 50	–	+	37
mtDNA 3644	mtDNA	Mitochondrial complex I (ND1)	–	(+)	38
mtDNA 3243*	mtDNA	Mitochondrial $tRNA^{Leu(UUR)}$	–	(+)	39
Negative studies					
Nogo	2p13-p13	Neurite outgrowth inhibitor	–	+	40
GAD1	2q31	Glutamate decarboxylase	–	–	41
DRD3	3q13	Dopamine D3 receptor	+	–	42
GSK3b	3q13.3	Glycogen synthase kinase 3-β	–	–	43–45
PHOX2B (PMX2B)	4p12	Transcription factor for DA neurons	+	–	46
ADRA2C	4p16.1	Adrenoceptor 2C	–	+	47
DAT1	5q14.3	Dopamine transporter	+	–	48
GABAAg2	5q31.1-q33.1	GABA-A receptor gamma 2 subunit	–	+	49
GABAAb2	5q34-q35	GABA-A receptor beta 2 subunit	–	+	49
NOTCH4	6p21.3	Notch signaling	+	–	50
DTNBP1	6p22.3	Dysbindin	+	+	51
TAAR6	6q23.2	Trace amine-associated receptor 6	+	+	52
ADRA1C	8p21	Adrenoceptor 1C	–	+	47
CHRNA2	8p21-22	Nicotinic acetylcholine receptor alpha 2	+	+	53
PIP5K2A	10p12.2	Phosphatydilinositol 5-phosphate kinase 2A	–	+	54
ADRA2A	10q24-q26	Adrenoceptor 2A	–	+	47
BDNF	11p13	Brain-derived neurotrophic factor	+	+	55–57
TPH1	11p15.3-q14	Tryptophan hydroxylase	+	+	58
DRD4	11p15.5	Dopamine D4 receptor	+	+	42
DRD2	11q23	Dopamine D2 receptor	+	+	42
FEZ1	11q24.2	Interaction with DISC1	+	–	59
NTF3	12p13	Neurotrophin 3	+	–	60
TPH2	12q21.1	Tryptophan hydroxylase 2	–	+	153
NOS1	12q24	Nitric oxide synthase 1	+	+	61
HTR2A	13q14-q21	Serotonin 2 A receptor	+	+	62
HTT	17q11.1	Serotonin transporter	+	+	63
ERDA1	17q21.3	A gene with triplet repeat	–	+	64
CTG18.1	18q21.1	A gene with triplet repeat	–	+	64
SYNJ1	21q22	Synaptojanin 1	+	+	65
ZDHHC8	22q11.21	Deleted in VCFS	+	+	66
XBP1	22q12	X-Box Binding Protein 1	+	+	67,68
MAOA	Xp11.23	Monoamine oxydase A	+	+	69
PCDH11Y	Yp11.2	Protocadherin 11, Y-Linked	–	–	70
Conflicting results					
NDUFV2	18p11	Mitochondrial complex I	+	+	71
IMPA2	18p11.2	Inositol monophosphatase 2	+	+	72,73

(+), Maternal inheritance; *, no statistical analysis was applied due to small number of post-mortem brain samples.

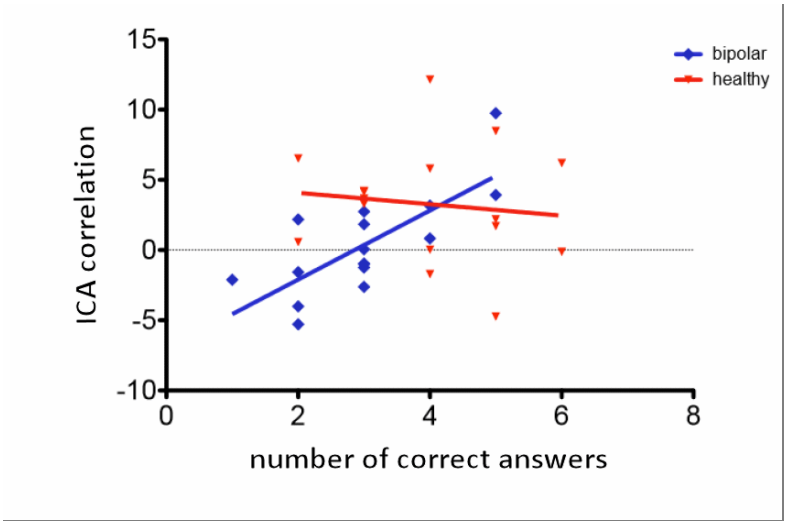


Figure X. ***Correlation between Auditory network and performance at visuospatial task.*** This picture shows the correlation among bipolar patients between ICA connectivity of Auditory Network and score at mental rotation task. You may see that this correlation is absent among healthy controls.

DIFFERENCES OF CONNECTIVITY BETWEEN GROUPS / VERBAL FLUENCY TASK
Less connected areas in patients compared to controls

LEFT 17

lG_and_S_cingulAnt to lG_cingulPostdorsal. Significance: 3.79

lG_front_sup to lG_orbital. Significance: 3.11

lG_cingulPostdorsal to lG_temp_supPlan_tempo. Significance: 3.55

lG_and_S_cingulAnt to lG_temporal_middle. Significance: 3.44

lG_octemp_medParahip to lS_circular_insula_ant. Significance: 3.48

lG_octemp_medParahip to lS_front_sup. Significance: 3.35

lG_insular_short to lS_intrapariet_and_P_trans. Significance: 3.58

lG_subcallosal to lS_intrapariet_and_P_trans. Significance: 3.81

lG_temporal_inf to lS_oc_sup_and_transversal. Significance: 3.21

lS_circular_insula_ant to lS_octemp_lat. Significance: 3.73

lS_front_sup to lS_octemp_lat. Significance: 3.52

lPole_temporal to lS_orbitalH_Shaped. Significance: 3.94

lG_orbital to lS_parieto_occipital. Significance: 3.29

lG_front_sup to lS_temporal_sup. Significance: 3.17

lG_and_S_subcentral to LPutamen. Significance: 3.18

lG_temporal_inf to LPutamen. Significance: 3.47

lS_intrapariet_and_P_trans to LAccumbens. Significance: 3.83

INTER- 42

lG_cingulPostdorsal to rG_and_S_cingulAnt. Significance: 3.22

lG_front_infTriangul to rG_and_S_cingulAnt. Significance: 3.24

LPallidum to rG_and_S_cingulAnt. Significance: 3.91

lS_octemp_lat to rG_and_S_cingulMidAnt. Significance: 3.65

lG_temp_supPlan_tempo to rG_and_S_cingulMidPost. Significance: 3.42

lS_octemp_lat to rG_and_S_cingulMidPost. Significance: 3.51

lS_temporal_sup to rG_and_S_cingulMidPost. Significance: 3.14

lG_and_S_frontomargin to rG_cingulPostdorsal. Significance: 3.13

lPole_temporal to rG_front_infOpercular. Significance: 3.50

lS_intrapariet_and_P_trans to rG_front_infTriangul. Significance: 4.40

LPutamen to rG_front_infTriangul. Significance: 3.93

lS_intrapariet_and_P_trans to rG_insular_short. Significance: 3.60

lG_front_sup to rG_octemp_latfusifor. Significance: 3.12

lS_calcarine to rG_octemp_medParahip. Significance: 3.28

lS_parieto_occipital to rG_pariet_infAngular. Significance: 3.21

lG_insular_short to rG_precuneus. Significance: 3.12

LPutamen to rG_rectus. Significance: 3.17

lG_and_S_frontomargin to rG_temp_supPlan_polar. Significance: 3.37

lS_oc_sup_and_transversal to rG_temp_supPlan_polar. Significance: 4.11

lS_parieto_occipital to rG_temp_supPlan_polar. Significance: 3.32

lG_temporal_inf to rG_temp_supPlan_tempo. Significance: 3.20

lS_orbitalH_Shaped to rG_temporal_inf. Significance: 3.49

LPutamen to rG_temporal_inf. Significance: 3.16

lG_cingulPostdorsal to rS_collat_transv_ant. Significance: 3.29

lS_cingulMarginalis to rS_collat_transv_ant. Significance: 4.55

lG_insular_short to rS_front_middle. Significance: 3.17

lG_temp_supPlan_tempo to rS_front_middle. Significance: 3.88

lS_calcarine to rS_front_middle. Significance: 3.25

lS_parieto_occipital to rS_front_middle. Significance: 3.12

lG_and_S_frontomargin to rS_front_sup. Significance: 3.20

lS_octemp_lat to rS_front_sup. Significance: 3.23

lG_temporal_middle to rS_precentralinfpart. Significance: 3.37

lS_intrapariet_and_P_trans to rS_precentralinfpart. Significance: 3.17

lG_and_S_frontomargin to rS_subparietal. Significance: 3.20

lG_subcallosal to rS_subparietal. Significance: 3.35

lG_and_S_cingulAnt to rS_temporal_sup. Significance: 3.13

lG_cingulPostdorsal to rS_temporal_sup. Significance: 3.59

lG_precuneus to rS_temporal_sup. Significance: 3.61

lG_and_S_cingulMidPost to RThalamus. Significance: 3.26

lS_precentralinfpart to RThalamus. Significance: 3.25

lG_temporal_inf to RPutamen. Significance: 3.56

lS_front_sup to RHippocampus. Significance: 3.34

RIGHT 12

rG_and_S_cingulMidAnt to rG_octemp_medLingual. Significance: 3.19

rG_and_S_subcentral to rG_octemp_medParahip. Significance: 3.19

rG_and_S_subcentral to rS_front_inf. Significance: 3.72

DX-DX

rG_front_infOpercular to rS_front_inf. Significance: 3.38

rG_pariet_infSupramar to rS_front_inf. Significance: 3.52
rG_pariet_infAngular to rS_front_middle. Significance: 3.12
rG_octemp_medParahip to rS_subparietal. Significance: 3.66
rG_and_S_cingulAnt to rS_temporal_sup. Significance: 3.61
rG_cingulPostdorsal to rS_temporal_sup. Significance: 3.19
rG_and_S_cingulMidPost to RThalamus. Significance: 3.23
rG_octemp_medParahip to RThalamus. Significance: 3.19

rG_octemp_latfusifor to RPallidum. Significance: 3.17

DIFFERENCES BETWEEN CONNECTIVITY IN RESTING STATE AND DURIG VERBAL TASK IN CONTROLS
Increased connectivity in control subjects

INTER- (144)
LHippocampus to rG_and_S_occipital_inf. Significance: 3.70
lG_and_S_frontomargin to rG_and_S_cingulAnt. Significance: 4.61
lG_and_S_subcentral to rG_and_S_cingulAnt. Significance: 4.02
lG_and_S_cingulMidPost to rG_and_S_cingulAnt. Significance: 3.43
lG_front_infOpercular to rG_and_S_cingulAnt. Significance: 5.64
lG_front_infTriangul to rG_and_S_cingulAnt. Significance: 4.30
lG_insular_short to rG_and_S_cingulAnt. Significance: 3.63
lG_occipital_middle to rG_and_S_cingulAnt. Significance: 4.74
lG_pariet_infSupramar to rG_and_S_cingulAnt. Significance: 5.90
lG_temp_supLateral to rG_and_S_cingulAnt. Significance: 3.89
lG_temp_supPlan_tempo to rG_and_S_cingulAnt. Significance: 3.38
lG_temporal_middle to rG_and_S_cingulAnt. Significance: 4.13
lS_cingulMarginalis to rG_and_S_cingulAnt. Significance: 3.72
lS_intrapariet_and_P_trans to rG_and_S_cingulAnt. Significance: 3.69
LHippocampus to rG_and_S_cingulAnt. Significance: 3.43
lG_cingulPostdorsal to rG_and_S_cingulMidAnt. Significance: 4.21
lG_pariet_infAngular to rG_and_S_cingulMidAnt. Significance: 6.26
lG_pariet_infAngular to rG_and_S_cingulMidPost. Significance: 3.16
lG_insular_short to rG_cingulPostdorsal. Significance: 5.59
lG_pariet_infSupramar to rG_cingulPostdorsal. Significance: 4.77
lG_temp_supPlan_tempo to rG_cingulPostdorsal. Significance: 3.63
lS_circular_insula_ant to rG_cingulPostdorsal. Significance: 3.27
rG_and_S_cingulMidAnt to rG_cingulPostdorsal. Significance: 3.42
lG_and_S_cingulAnt to rG_front_infOpercular. Significance: 3.96
lG_cingulPostdorsal to rG_front_infOpercular. Significance: 4.97
lG_pariet_infAngular to rG_front_infOpercular. Significance: 3.16

lG_rectus to rG_front_infOpercular. Significance: 4.92
lPole_temporal to rG_front_infOpercular. Significance: 3.15
lG_and_S_cingulAnt to rG_front_infTriangul. Significance: 3.32
lG_and_S_cingulMidAnt to rG_front_infTriangul. Significance: 3.20
lG_temp_supPlan_polar to rG_front_middle. Significance: 3.29
lG_and_S_transv_frontopol to rG_front_sup. Significance: 3.99
lG_and_S_cingulAnt to rG_insular_short. Significance: 4.35
lG_cingulPostdorsal to rG_insular_short. Significance: 7.12
lG_pariet_infAngular to rG_insular_short. Significance: 3.19

lG_precuneus to rG_insular_short. Significance: 3.54

lS_temporal_sup to rG_insular_short. Significance: 3.44

LThalamus to rG_insular_short. Significance: 3.73
lG_and_S_cingulAnt to rG_occipital_middle. Significance: 3.42
lG_cingulPostdorsal to rG_occipital_middle. Significance: 3.27
lG_and_S_cingulMidPost to rG_occipital_sup. Significance: 3.52
lG_cingulPostdorsal to rG_octemp_latfusifor. Significance: 3.87
LHippocampus to rG_octemp_latfusifor. Significance: 4.13
lG_cingulPostdorsal to rG_octemp_medLingual. Significance: 4.37
lG_and_S_occipital_inf to rG_octemp_medParahip. Significance: 3.23

lG_cingulPostdorsal to rG_orbital. Significance: 6.00

lG_precuneus to rG_orbital. Significance: 4.68
lG_insular_short to rG_pariet_infAngular. Significance: 4.06
lG_occipital_sup to rG_pariet_infAngular. Significance: 3.68
lG_pariet_infSupramar to rG_pariet_infAngular. Significance: 3.26
lG_precuneus to rG_pariet_infAngular. Significance: 3.24
lG_and_S_cingulAnt to rG_pariet_infSupramar. Significance: 8.20
lG_cingulPostdorsal to rG_pariet_infSupramar. Significance: 8.68
lG_front_sup to rG_pariet_infSupramar. Significance: 4.72

lG_pariet_infAngular to rG_pariet_infSupramar. Significance: 3.85
lG_precuneus to rG_pariet_infSupramar. Significance: 4.74

lG_rectus to rG_pariet_infSupramar. Significance: 3.93
lG_temporal_middle to rG_pariet_infSupramar. Significance: 4.19
lS_parieto_occipital to rG_pariet_infSupramar. Significance: 3.14
lS_subparietal to rG_pariet_infSupramar. Significance: 5.31
lS_temporal_sup to rG_pariet_infSupramar. Significance: 4.95

lG_front_middle to rG_postcentral. Significance: 3.23
lG_pariet_infSupramar to rG_postcentral. Significance: 4.41

lG_and_S_cingulAnt to rG_precuneus. Significance: 4.19

lG_front_sup to rG_precuneus. Significance: 3.49

lG_orbital to rG_precuneus. Significance: 3.15

lG_and_S_subcentral to rG_rectus. Significance: 3.18

lG_front_infOpercular to rG_rectus. Significance: 3.92

lG_front_infTriangul to rG_rectus. Significance: 4.11

lG_temp_supLateral to rG_rectus. Significance: 3.23
lS_octemp_med_and_Lingual to rG_rectus. Significance: 3.27

LPutamen to rG_rectus. Significance: 3.11
lG_and_S_cingulAnt to rG_temp_supLateral. Significance: 4.10
lG_cingulPostdorsal to rG_temp_supLateral. Significance: 4.92

lG_rectus to rG_temp_supLateral. Significance: 3.39
lG_and_S_cingulAnt to rG_temp_supPlan_polar. Significance: 3.44
lG_cingulPostdorsal to rG_temp_supPlan_polar. Significance: 3.20

lG_orbital to rG_temp_supPlan_polar. Significance: 3.61
lG_and_S_cingulAnt to rG_temp_supPlan_tempo. Significance: 3.98
lG_cingulPostdorsal to rG_temp_supPlan_tempo. Significance: 3.40
lG_cingulPostdorsal to rG_temporal_inf. Significance: 3.34

LHippocampus to rG_temporal_inf. Significance: 3.18
lG_and_S_cingulAnt to rG_temporal_middle. Significance: 3.48
lG_cingulPostdorsal to rG_temporal_middle. Significance: 3.11
lG_Ins_lg_and_S_cent_ins to rG_temporal_middle. Significance: 3.35
lG_insular_short to rG_temporal_middle. Significance: 3.26

lG_front_infOpercular to rS_calcarine. Significance: 3.95

lG_parietal_sup to rS_calcarine. Significance: 3.15

lG_front_infTriangul to rS_central. Significance: 3.67

lG_cingulPostdorsal to rS_cingulMarginalis. Significance: 4.06
lG_and_S_frontomargin to rS_circular_insula_ant. Significance: 3.86
lG_cingulPostdorsal to rS_circular_insula_ant. Significance: 3.14
lS_temporal_sup to rS_circular_insula_ant. Significance: 3.77

LThalamus to rS_circular_insula_ant. Significance: 3.23
lG_and_S_cingulAnt to rS_circular_insula_inf. Significance: 3.44
lG_cingulPostdorsal to rS_circular_insula_inf. Significance: 5.09
lG_front_sup to rS_circular_insula_inf. Significance: 3.93

lG_orbital to rS_circular_insula_inf. Significance: 3.31
lG_cingulPostdorsal to rS_circular_insula_sup. Significance: 3.40
lG_cingulPostdorsal to rS_front_middle. Significance: 5.08
lG_pariet_infAngular to rS_front_middle. Significance: 3.31

lG_precuneus to rS_front_middle. Significance: 3.56

lS_subparietal to rS_front_middle. Significance: 4.46

lG_front_sup to rS_front_sup. Significance: 3.54

lG_pariet_infAngular to rS_front_sup. Significance: 3.70

lG_precentral to rS_front_sup. Significance: 3.40

lG_temporal_middle to rS_front_sup. Significance: 3.66
lS_circular_insula_sup to rS_front_sup. Significance: 3.90
lG_and_S_cingulAnt to rS_intrapariet_and_P_trans. Significance: 4.82
lG_cingulPostdorsal to rS_intrapariet_and_P_trans. Significance: 4.37
lG_front_sup to rS_intrapariet_and_P_trans. Significance: 3.96
lG_precuneus to rS_intrapariet_and_P_trans. Significance: 3.55
lG_temporal_middle to rS_intrapariet_and_P_trans. Significance: 3.51
lS_subparietal to rS_intrapariet_and_P_trans. Significance: 4.01
lG_cingulPostdorsal to rS_oc_sup_and_transversal. Significance: 3.58
lG_octemp_medParahip to rS_oc_temp_med_and_Lingual. Significance: 3.46
lS_octemp_med_and_Lingual to rS_oc_temp_med_and_Lingual. Significance: 3.11
lG_front_infOpercular to rS_orbital_medolfact. Significance: 3.93
lG_front_infTriangul to rS_orbital_medolfact. Significance: 3.35
lS_temporal_sup to rS_orbital_medolfact. Significance: 3.12
lG_and_S_cingulAnt to rS_precentralinfpart. Significance: 3.21
lG_cingulPostdorsal to rS_precentralinfpart. Significance: 4.36

lG_insular_short to rS_subparietal. Significance: 5.56

lG_temp_supPlan_tempo to rS_subparietal. Significance: 3.55
lG_and_S_cingulAnt to rS_temporal_sup. Significance: 3.20
lG_cingulPostdorsal to rS_temporal_sup. Significance: 5.72

lG_insular_short to rS_temporal_sup. Significance: 4.05

lG_precuneus to rS_temporal_sup. Significance: 3.98

lG_rectus to rS_temporal_sup. Significance: 3.65

lG_cingulPostdorsal to RThalamus. Significance: 5.78
lG_Ins_lg_and_S_cent_ins to RThalamus. Significance: 3.27

lG_orbital to RThalamus. Significance: 3.34

lG_precuneus to RThalamus. Significance: 3.35

lG_rectus to RThalamus. Significance: 3.24

lS_temporal_sup to RThalamus. Significance: 3.78

lG_cingulPostdorsal to RPutamen. Significance: 4.49

lG_rectus to RPutamen. Significance: 3.89

lG_cingulPostdorsal to RPallidum. Significance: 3.82

lG_rectus to RPallidum. Significance: 3.64

lG_front_infOpercular to RCaudate. Significance: 3.79

lG_pariet_infSupramar to RCaudate. Significance: 3.13

lG_occipital_middle to RAccumbens. Significance: 3.14

lG_temp_supLateral to RAccumbens. Significance: 3.36

lS_temporal_sup to RAccumbens. Significance: 4.70

RIGHT

rG and S cingul MidAnt to rG cingulPostdorsal. Test stat: 3.42

rG_and_S_cingulAnt to rG_front_infOpercular. Test stat: 3.43

rG_cingulPostdorsal to rG_front_infOpercular. Test stat: 5.94

rG_and_S_cingulAnt to rG_insular_short. Test stat: 4.09

rG_cingulPostdorsal to rG_insular_short. Test stat: 3.87

rG_and_S_cingulAnt to rG_occipital_middle. Test stat: 4.18

rG_and_S_cingulAnt to rG_occipital_sup. Test stat: 3.47

rG_octemp_latfusifor to rG_octemp_medParahip. Test stat: 3.23

rG_and_S_cingulAnt to rG_pariet_infAngular. Test stat: 3.19

rG_and_S_cingulMidAnt to rG_pariet_infAngular. Test stat: 5.79

rG_and_S_cingulMidPost to rG_pariet_infAngular. Test stat: 3.70

rG_front_infOpercular to rG_pariet_infAngular. Test stat: 5.81

rG_insular_short to rG_pariet_infAngular. Test stat: 3.85

rG_and_S_cingulAnt to rG_pariet_infSupramar. Test stat: 6.34

rG_cingulPostdorsal to rG_pariet_infSupramar. Test stat: 6.66

rG_front_sup to rG_pariet_infSupramar. Test stat: 4.73

rG_pariet_infAngular to rG_pariet_infSupramar. Test stat: 6.75

rG_and_S_cingulMidAnt to rG_postcentral. Test stat: 3.11

rG_octemp_medParahip to rG_postcentral. Test stat: 3.56

rG_pariet_infSupramar to rG_postcentral. Test stat: 7.25

rG_and_S_cingulAnt to rG_precentral. Test stat: 3.11

rG_and_S_cingulAnt to rG_precuneus. Test stat: 3.80

rG_front_infTriangul to rG_precuneus. Test stat: 3.18

rG_postcentral to rG_precuneus. Test stat: 3.37

rG_and_S_subcentral to rG_rectus. Test stat: 3.42

rG_and_S_cingulAnt to rG_temp_supLateral. Test stat: 4.85

rG_cingulPostdorsal to rG_temp_supLateral. Test stat: 3.70

rG_pariet_infAngular to rG_temp_supLateral. Test stat: 3.26

rG_rectus to rG_temp_supLateral. Test stat: 3.32

rG_front_sup to rG_temp_supPlan_polar. Test stat: 4.46

rG_insular_short to rG_temporal_middle. Test stat: 3.28

rG_and_S_cingulAnt to rS_circular_insula_inf. Test stat: 3.15

rG_front_sup to rS_circular_insula_inf. Test stat: 3.95

rG_and_S_cingulAnt to rS_front_middle. Test stat: 3.41

rG_cingulPostdorsal to rS_front_middle. Test stat: 3.51

rG_pariet_infAngular to rS_front_middle. Test stat: 3.79

rG_temporal_inf to rS_oc_temp_med_and_Lingual. Test stat: 3.19

rG_front_sup to rS_orbital_medolfact. Test stat: 3.28

rG_and_S_cingulAnt to rS_precentralinfpart. Test stat: 3.12

rG_cingulPostdorsal to rS_precentralinfpart. Test stat: 3.37

rG_front_infOpercular to rS_subparietal. Test stat: 4.09

rG_front_middle to rS_subparietal. Test stat: 3.26

rG_insular_short to rS_subparietal. Test stat: 4.33

rG_orbital to rS_subparietal. Test stat: 3.80

rG_pariet_infSupramar to rS_subparietal. Test stat: 7.47

rS_circular_insula_ant to rS_subparietal. Test stat: 3.33

rS_front_middle to rS_subparietal. Test stat: 3.13

rS_oc_sup_and_transversal to rS_subparietal. Test stat: 3.23

rG_and_S_cingulAnt to rS_temporal_sup. Test stat: 3.43

rG_cingulPostdorsal to rS_temporal_sup. Test stat: 3.89

rG_pariet_infAngular to rS_temporal_sup. Test stat: 3.55

rG_parietal_sup to rS_temporal_sup. Test stat: 4.75

rG_precuneus to rS_temporal_sup. Test stat: 3.49

rG_rectus to RThalamus. Test stat: 3.20

rS_oc_sup_and_transversal to RThalamus. Test stat: 3.51

rG_front_infOpercular to RCaudate. Test stat: 3.21

rG_pariet_infSupramar to RCaudate. Test stat: 3.43

rS_intrapariet_and_P_trans to RCaudate. Test stat: 3.11

rS_precentralinfpart to RCaudate. Test stat: 3.31

rG_rectus to RPallidum. Test stat: 3.91

rG_parietal_sup to RHippocampus. Test stat: 3.10

rG_temporal_inf to RAmygdala. Test stat: 3.23

rG_temp_supLateral to RAccumbens. Test stat: 3.46

rS_circular_insula_inf to RAccumbens. Test stat: 3.49

RThalamus to RAccumbens. Test stat: 3.39

LEFT

lG_and_S_frontomargin to lG_and_S_cingulAnt. Test stat: 3.32
lG_and_S_subcentral to lG_and_S_cingulAnt. Test stat: 3.47
lG_and_S_frontomargin to lG_cingulPostdorsal. Test stat: 3.39
lG_and_S_subcentral to lG_cingulPostdorsal. Test stat: 3.84
lG_and_S_cingulMidAnt to lG_cingulPostdorsal. Test stat: 4.77
lG_and_S_cingulMidPost to lG_cingulPostdorsal. Test stat: 3.17
lG_and_S_cingulAnt to lG_front_infOpercular. Test stat: 4.03
lG_cingulPostdorsal to lG_front_infOpercular. Test stat: 4.31
lG_and_S_cingulAnt to lG_front_infTriangul. Test stat: 3.78
lG_cingulPostdorsal to lG_Ins_lg_and_S_cent_ins. Test stat: 3.61

lG_and_S_cingulAnt to lG_insular_short. Test stat: 3.41

lG_cingulPostdorsal to lG_insular_short. Test stat: 9.28
lG_and_S_cingulAnt to lG_occipital_middle. Test stat: 4.04
lG_cingulPostdorsal to lG_occipital_middle. Test stat: 3.67
lG_cingulPostdorsal to lG_octemp_latfusifor. Test stat: 3.72

lG_cingulPostdorsal to lG_orbital. Test stat: 3.75

lG_insular_short to lG_pariet_infAngular. Test stat: 3.13

lG_occipital_sup to lG_pariet_infAngular. Test stat: 3.47
lG_and_S_cingulAnt to lG_pariet_infSupramar. Test stat: 6.26
lG_cingulPostdorsal to lG_pariet_infSupramar. Test stat: 6.98

lG_front_sup to lG_pariet_infSupramar. Test stat: 3.72
lG_pariet_infAngular to lG_pariet_infSupramar. Test stat: 5.96

lG_cingulPostdorsal to lG_parietal_sup. Test stat: 3.67

lG_and_S_cingulAnt to lG_precuneus. Test stat: 3.15

lG_insular_short to lG_precuneus. Test stat: 3.53

lG_orbital to lG_precuneus. Test stat: 5.41

lG_front_infOpercular to lG_rectus. Test stat: 5.22

lG_front_infTriangul to lG_rectus. Test stat: 3.17

lG_pariet_infSupramar to lG_rectus. Test stat: 5.97
lG_and_S_cingulAnt to lG_temp_supLateral. Test stat: 4.19
lG_cingulPostdorsal to lG_temp_supLateral. Test stat: 4.88
lG_cingulPostdorsal to lG_temp_supPlan_tempo. Test stat: 4.40
lG_and_S_cingulAnt to lG_temporal_middle. Test stat: 5.00
lG_cingulPostdorsal to lG_temporal_middle. Test stat: 3.21
lG_pariet_infSupramar to lG_temporal_middle. Test stat: 3.34

lG_front_infTriangul to lPole_temporal. Test stat: 3.10

lG_front_infOpercular to lS_calcarine. Test stat: 3.15

lG_front_infTriangul to lS_calcarine. Test stat: 3.93
lG_cingulPostdorsal to lS_circular_insula_ant. Test stat: 3.23

lG_occipital_sup to lS_circular_insula_ant. Test stat: 3.11
lG_cingulPostdorsal to lS_circular_insula_inf. Test stat: 3.63

lG_and_S_cingulAnt to lS_front_inf. Test stat: 4.89

lG_pariet_infSupramar to lS_front_middle. Test stat: 4.12
lG_and_S_cingulAnt to lS_intrapariet_and_P_trans. Test stat: 4.29
lG_temporal_inf to lS_oc_sup_and_transversal. Test stat: 3.26

lS_circular_insula_ant to lS_octemp_lat. Test stat: 3.43

lS_front_sup to lS_octemp_lat. Test stat: 3.61

lG_precentral to lS_orbital_medolfact. Test stat: 3.82

lG_precentral to lS_orbitalH_Shaped. Test stat: 4.06
lS_oc_sup_and_transversal to lS_parieto_occipital. Test stat: 4.10
lS_orbitalH_Shaped to lS_parieto_occipital. Test stat: 3.56

lG_and_S_cingulAnt to lS_postcentral. Test stat: 3.41

lG_cingulPostdorsal to lS_postcentral. Test stat: 4.81

lG_rectus to lS_postcentral. Test stat: 3.45
lG_cingulPostdorsal to lS_precentralinfpart. Test stat: 3.28

lG_pariet_infSupramar to lS_subparietal. Test stat: 3.77

lS_postcentral to lS_subparietal. Test stat: 3.12

lG_insular_short to lS_temporal_sup. Test stat: 3.91
lG_pariet_infSupramar to lS_temporal_sup. Test stat: 3.83

lG_precuneus to lS_temporal_sup. Test stat: 3.16

lG_cingulPostdorsal to LThalamus. Test stat: 3.90

lG_front_infTriangul to LThalamus. Test stat: 3.16

lG_Ins_lg_and_S_cent_ins to LThalamus. Test stat: 3.32

lG_temp_supLateral to LThalamus. Test stat: 3.17

lG_front_infTriangul to LCaudate. Test stat: 4.57

lG_cingulPostdorsal to LPutamen. Test stat: 3.12

lG_and_S_occipital_inf to LHippocampus. Test stat: 5.14

lG_and_S_occipital_inf to LAccumbens. Test stat: 3.73

MOST CONNECTED NETWORKS DURING VERBAL FLUENCY TASK VS. RESTING STATE, IN CONTROLS COMPARED TO PATIENTS.

RIGHT 6

rG_front_infOpercular to rS_front_inf. Test stat: 3.84

rG_pariet_infAngular to rS_front_middle. Test stat: 3.11

rS_front_middle to rS_subparietal. Test stat: 3.27

rG_precuneus to rS_temporal_sup. Test stat: 3.21

rG_postcentral to RThalamus. Test stat: 3.58

rS_intrapariet_and_P_trans to RCaudate. Test stat: 3.20

INTER- 21

lG_front_infOpercular to rG_and_S_cingulAnt. Test stat: 4.11

lG_front_infTriangul to rG_and_S_cingulAnt. Test stat: 3.12

lG_temporal_middle to rG_and_S_cingulAnt. Test stat: 3.51

lS_subparietal to rG_and_S_cingulAnt. Test stat: 3.17

LPallidum to rG_and_S_cingulAnt. Test stat: 3.12

lG_cingulPostdorsal to rG_front_infOpercular. Test stat: 3.17

lPole_temporal to rG_front_infOpercular. Test stat: 3.27

lS_orbitalH_Shaped to rG_postcentral. Test stat: 3.48

lG_and_S_cingulAnt to rG_precuneus. Test stat: 3.32

lG_front_infTriangul to rG_rectus. Test stat: 3.82

lG_octemp_latfusifor to rG_rectus. Test stat: 3.16

lS_octemp_med_and_Lingual to rG_rectus. Test stat: 3.26

lG_cingulPostdorsal to rG_temporal_middle. Test stat: 3.34

lG_cingulPostdorsal to rS_circular_insula_inf. Test stat: 3.27

lS_subparietal to rS_front_middle. Test stat: 3.95

lG_front_infOpercular to rS_orbital_medolfact. Test stat: 3.11

lS_temporal_sup to rS_orbital_medolfact. Test stat: 3.48

lG_cingulPostdorsal to rS_temporal_sup. Test stat: 4.51

lG_cingulPostdorsal to RThalamus. Test stat: 3.11

lG_front_infOpercular to RCaudate. Test stat: 3.43

lG_and_S_cingulAnt to RPallidum. Test stat: 3.42

LEFT 18

lG_and_S_cingulAnt to lG_cingulPostdorsal. Test stat: 4.01

lG_and_S_cingulAnt to lG_front_infOpercular. Test stat: 3.25

lG_cingulPostdorsal to lG_front_infOpercular. Test stat: 3.54

lG_cingulPostdorsal to lG_insular_short. Test stat: 4.87

lG_cingulPostdorsal to lG_octemp_latfusifor. Test stat: 3.52

lG_cingulPostdorsal to lG_orbital. Test stat: 3.29

lG_and_S_cingulAnt to lG_precuneus. Test stat: 3.74

lG_cingulPostdorsal to lG_precuneus. Test stat: 3.22

lG_orbital to lG_precuneus. Test stat: 3.14

lG_front_infOpercular to lG_rectus. Test stat: 3.74

lG_and_S_cingulAnt to lG_temporal_middle. Test stat: 4.62

lG_front_infTriangul to lPole_temporal. Test stat: 4.23

lG_and_S_cingulAnt to lS_front_inf. Test stat: 3.19

lG_cingulPostdorsal to lS_front_inf. Test stat: 3.13

lG_rectus to lS_front_sup. Test stat: 3.13

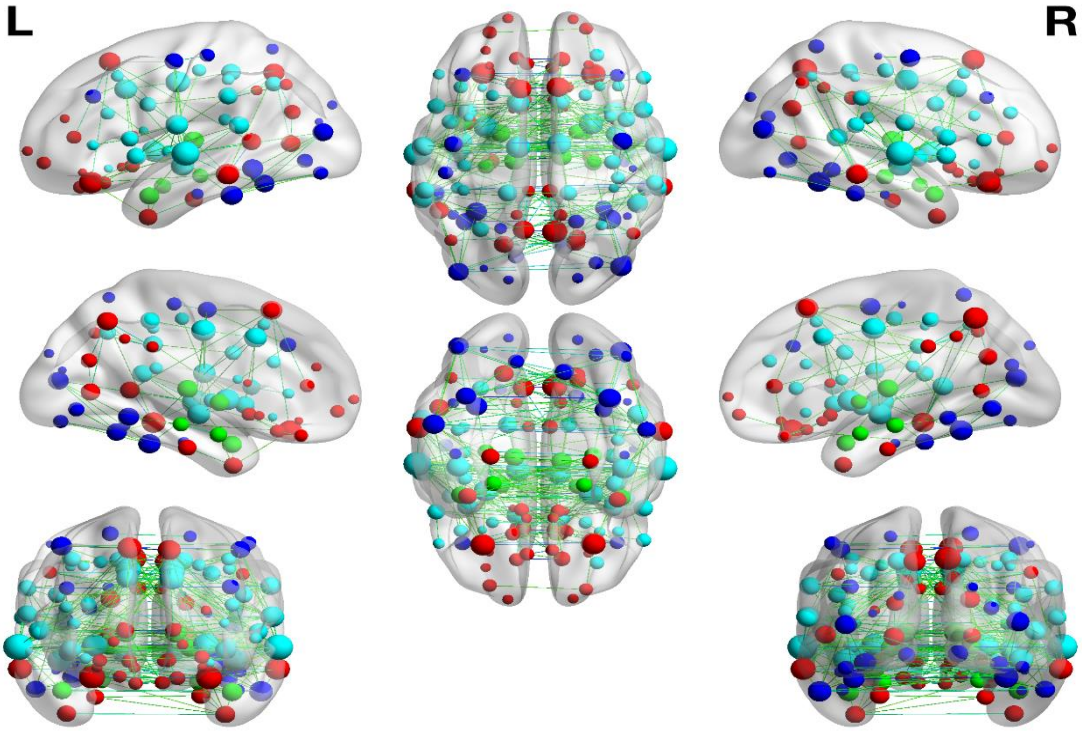
lG_and_S_cingulAnt to lS_intrapariet_and_P_trans. Test stat: 3.61

lG_cingulPostdorsal to LThalamus. Test stat: 3.15

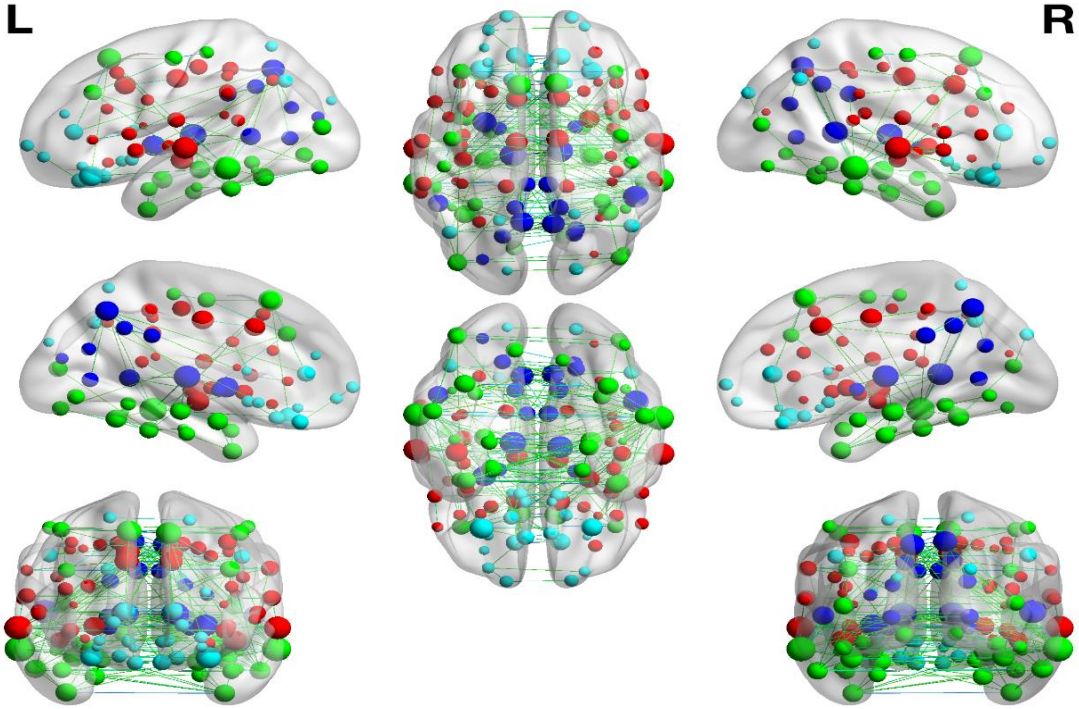
lG_and_S_cingulAnt to LPallidum. Test stat: 3.58

BRAIN NETWORK

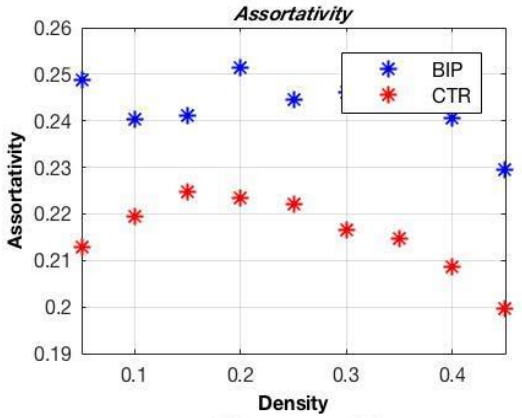
CONTROLS

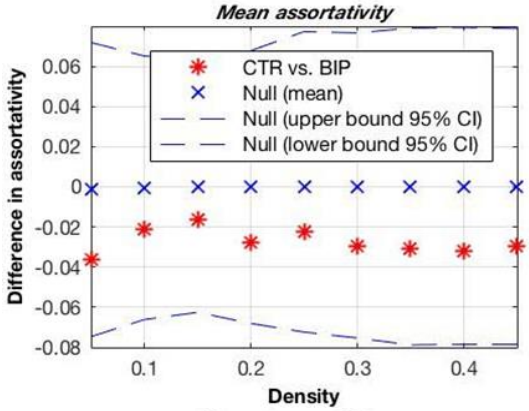


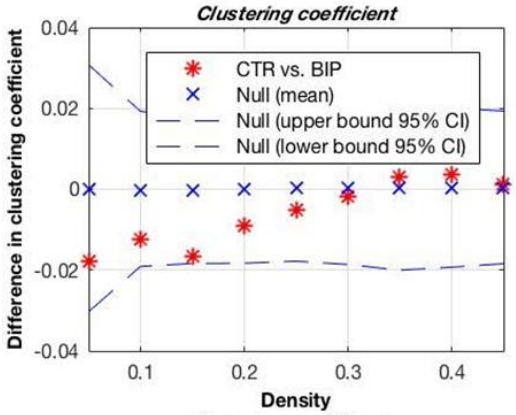
PATIENTS

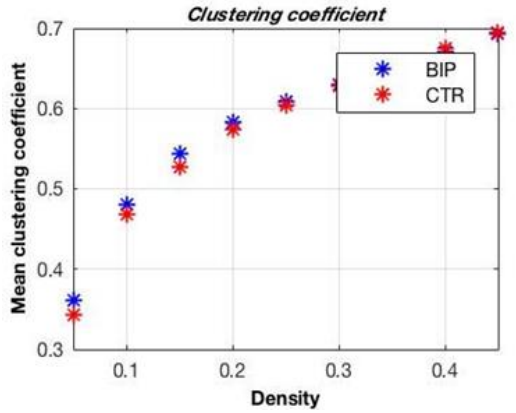


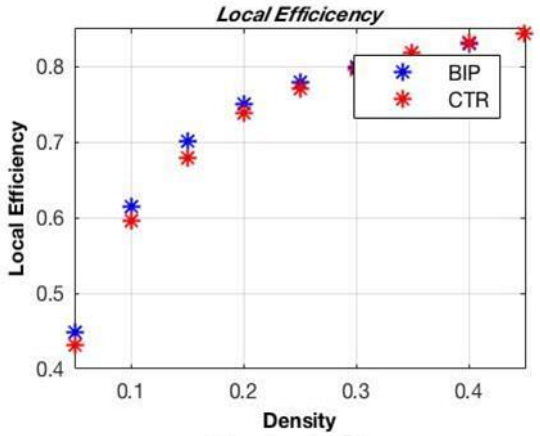
Green lines represent connections. Spheres represent nodes: different colours (green, red, light and dark blue) indicate different modules.

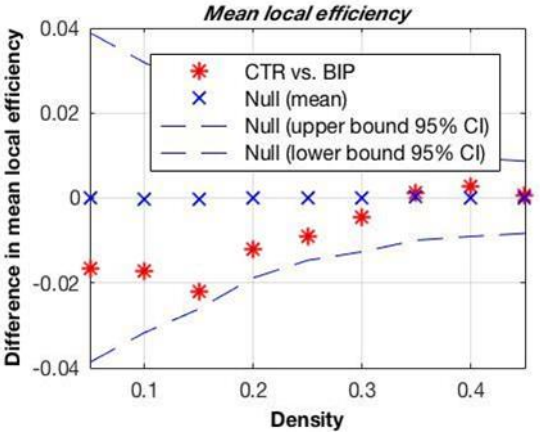

Assortativity
Assortativity
Density
BIP
CTR
0.26
0.25
0.24
0.23
0.22
0.21
0.2
0.19
0.1
0.2
0.3
0.4

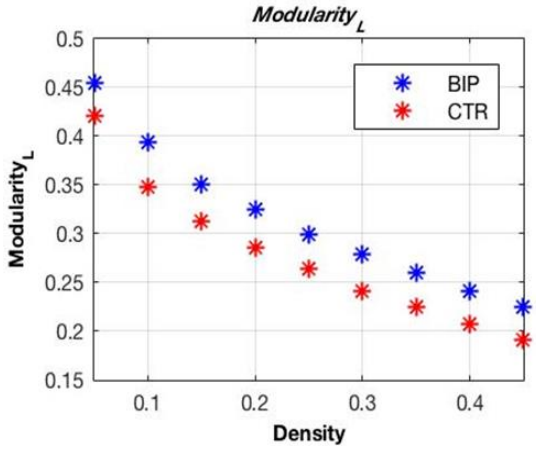

Mean assortativity
Difference in assortativity
Density
CTR vs. BIP
Null (mean)
Null (upper bound 95% CI)
Null (lower bound 95% CI)
0.06
0.04
0.02
0
-0.02
-0.04
-0.06
-0.08
0.1
0.2
0.3
0.4

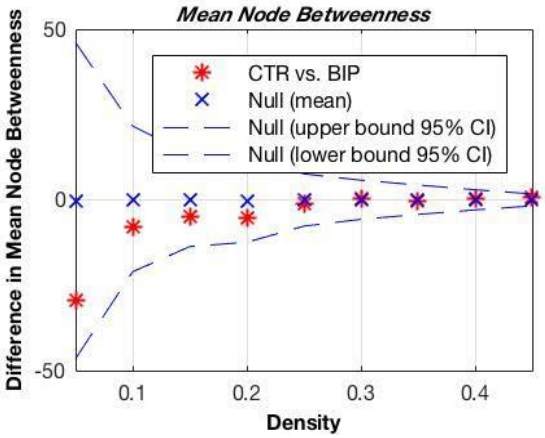

Clustering coefficient
Difference in clustering coefficient
Density
CTR vs. BIP
Null (mean)
Null (upper bound 95% CI)
Null (lower bound 95% CI)
0.04
0.02
0
-0.02
-0.04
0.1
0.2
0.3
0.4

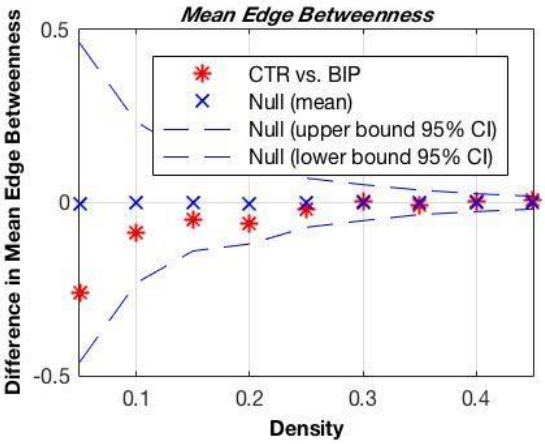

Clustering coefficient
Mean clustering coefficient
Density
BIP
CTR
0.7
0.6
0.5
0.4
0.3
0.1
0.2
0.3
0.4


Local Efficicency
Local Efficiency
Density
BIP
CTR
0.4
0.5
0.6
0.7
0.8
0.1
0.2
0.3
0.4


Mean local efficiency
Difference in mean local efficiency
Density
CTR vs. BIP
Null (mean)
Null (upper bound 95% CI)
Null (lower bound 95% CI)
0.04
0.02
0
-0.02
-0.04
0.1
0.2
0.3
0.4


Modularity L
Modularity L
Density
BIP
CTR
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.2
0.3
0.4


Mean Node Betweenness
Difference in Mean Node Betweenness
50
0
-50
0.1
0.2
0.3
0.4
Density
CTR vs. BIP
Null (mean)
Null (upper bound 95% CI)
Null (lower bound 95% CI)


Mean Edge Betweenness
Difference in Mean Edge Betweenness
0.5
0
-0.5
0.1
0.2
0.3
0.4
Density
CTR vs. BIP
Null (mean)
Null (upper bound 95% CI)
Null (lower bound 95% CI)

Subject	Group	AGE (y)	SCHOOLING (y)	HEIGHT (m)	WEIGHT (kg)	HANDEDNESS	Flu	Flu+	FluRep	FluIntr	sMRT	sMRT_acc		
101	control	36	30	1.67	52	right	4	6	0	4	6	100.00		
102	control	41	16	1.63	69	right	9	9	0	2	4	66.67		
103	control	41	18	1.68	89	right	10	10	0	0	3	50.00		
104	control	49	21	1.56	55	right	9	10	0	2	4	66.67		
105	control	45	13	1.54	70.5	right	5	5	0	0	6	100.00		
106	control	65	18	1.7	56	right	10	10	0	0	5	83.33		
107	control	65	13	1.65	58	right	4	5	0	1	2	33.33		
108	control	66	11	1.68	72	right	3	4	0	1	4	66.67		
109	control	69	18	1.73	72	right	7	7	0	1	3	50.00		
110	control	50	18	1.85	84	right	3	4	4	1	4	66.67		
111	control	44	13	1.72	80	right	10	10	0	1	5	83.33		
112	control	52	18	1.83	85	right	8	8	3	1	2	33.33		
113	control	35	19	1.62	63	right	3	3	0	1	5	83.33		
114	control	47	13	1.7	67	right	7	11	1	7	5	83.33		
115	control	66	5	1.73	64	right	3	3	0	0	3	50.00		
116	control	48	23	1.75	74	right	9	10	0	2	3	50.00		
1	patient	46	13	1.6	76	right	4	5	1	3	4	66.67		
2	patient	42	16	1.73	57	right	9	10	0	1	3	50.00		
3	patient	45	13	1.82	81	right	1	1	0	4	3	50.00		
4	patient	52	11	1.77	75	right	8	9	0	1	2	33.33		
5	patient	40	13	1.63	61	right	5	6	0	2	3	50.00		
6	patient	54	12	1.82	90	right	6	6	1	3	3	50.00		
7	patient	37	18	1.68	59	right	13	13	1	0	5	83.33		
8	patient	42	18	1.65	72	right	6	7	0	1	5	83.33		
9	patient	71	8	1.65	75	right	8	8	0	5	2	33.33		
10	patient	50	17	1.75	75	right	8	9	1	1	1	16.67		
11	patient	47	13	1.55	70	right	5	5	0	0	4	66.67		
12	patient	67	13	1.85	80	right	4	5	0	1	3	50.00		
13	patient	65	5	1.61	70	right	3	3	0	0	2	33.33		
14	patient	71	7	1.65	70	right	6	6	1	0	3	50.00		
15	patient	59	8	1.55	70	right	5	5	0	0	3	50.00		
16	patient	64	8	1.64	75	right	3	3	0	2	2	33.33		
17	patient	66	17	1.6	59	right	9	10	0	1	3	50.00		
18	patient	63	15	1.78	75	right								