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State of Art of Serum Brain-Derived Neurotrophic Factor in Schizophrenia

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1. Introduction

Schizophrenia is a common severe psychiatric disorder which affects approximately 1% of the world population. Imaging studies and postmortem analysis have clearly shown that schizophrenia is not a mere functional disorder, but rather includes several histological abnormalities in various areas of the brain. Today, deficits in brain development or a malfunction in the dopaminergic system are considered the leading hallmarks of schizophrenia (Fatemi & Folsom, 2009; Howes & Kapur, 2009; Iritani, 2007).

Although the pathogenesis of schizophrenia remains still unresolved, it is now clear that this disorder is the result of a complex interplay between inheritable genetic mutations in a large number of genes (a few common mutations with a small effect combined with many rare ones with a stronger effect), various environmental influences and epigenetic effects (van OS & Kapur, 2009; Owen et al., 2009; O'Donnel et al., 2009; Psychiatric GWAS Consortium [PGC], 2009; Roth et al., 2009). Over the years, multiple theories have been proposed to explain how these factors may generate schizophrenia. The different models proposed include principally the neurodevelopmental and the dopaminergic hypotheses which have been reviewed elsewhere (Fatemi & Folsom, 2009; Howes & Kapur, 2009). These two hypotheses may not necessarily be mutually exclusive as, for instance, a local dysfunction in dopaminergic neurotransmission may be the result of a failed development. Moreover, a number of studies pointed to the role of neurotrophins in the pathogenesis of schizophrenia. Neurotrophins are a small group of secreted dimeric proteins that affect the development of the nervous system in all vertebrates' species and are involved in the development and maturation of several brain networks including the dopaminergic system (Buckley et al. 2007; Shoval & Weizman, 2005; Thome et al. 1998). Brain-Derived Neurotrophic Factor (BDNF) is the most widely distributed neurotrophin in the central nervous system (CNS) and is known to exert growth and trophic effects able to support many aspects of neuronal development including axonal growth and connectivity (Segal et al., 1995), neuronal survival and apoptosis (Segal et al., 1997), and formation of dopaminergic-related systems. Furthermore, BDNF has a dynamic effect on synaptic organization, promoting long-term

changes of synaptic transmission (Shen et al., 1997), as well as learning and memory processes (Yamada et al., 2002). For these reasons many studies investigated the role of BDNF in the pathophysiology of schizophrenia but their findings resulted contradictory. For example, some postmortem studies conducted on schizophrenia brains showed elevated BDNF levels in the anterior cingulate, hippocampus (Takahashi et al., 2000) and cerebral cortex (Durany et al., 2001), whereas others found decreased BDNF levels in the hippocampus (Durany et al., 2001) and prefrontal cortex (Weickert et al., 2003, 2005).

Interestingly, in both humans and rodents, BDNF is present not only in the brain but also in peripheral tissues and especially, in the blood (Pruunsild et al., 2007; Aid et al., 2007). The origin of circulating BDNF has been debated as this neurotrophin is produced by many different body tissues and epithelia, including smooth muscle cells of blood vessels (Donovan et al., 1995). However, it has been demonstrated that radiolabeled BDNF injected in the jugular vein or in the brain ventricle readily crosses the blood-brain barrier in both directions (Pan et al., 1998) and can be taken up by platelets that function as storage and release system (Karege et al., 2005). In addition, it has been shown that physical exercise induces an increase of serum BDNF levels which is contributed by 70% from the brain (Rasmussen et al., 2009). Thus, measurement of circulating BDNF is very attractive, because it may provide information on brain functioning and blood samples are largely available and may be drawn non-invasively from living subjects as frequently as necessary. BDNF can be measured using simple enzyme linked immunoadsorbent assays (ELISA) that are commercially available and recent methodological studies have pointed out the possibility to obtain reliable measures of BDNF in serum preparations with stable values over several months of serum storage at -20°C, while in contrast, there is high variability in the measures of BDNF in whole blood or plasma because of the presence of release from platelets and degradation processes that are active even during storage (Elfving et al., 2009; Trajkovska et al., 2007). For these reasons, there is currently a great interest to validate the use of serum BDNF as possible biomarker in brain diseases, including psychiatric illnesses (for a recent meta-analysis of serum BDNF in depression see: Sen et al., 2008).

To assess if BDNF can represent a good biomarker in schizophrenia, a growing number of studies compared BDNF serum levels between patients with schizophrenia and healthy control subjects but unfortunately, with controversial results. Indeed, several investigators found a significant decrease in serum BDNF concentrations (Carlino et al., 2011; Chen et al., 2009; Grillo et al., 2007; Ikeda et al., 2008; Jindal et al., 2010; Pirildar et al., 2004; Rizos et al., 2008; Shimizu et al., 2002; Tan et al., 2005a, 2005b; Toyooka et al., 2002; Xiu et al., 2009; Zhang et al., 2007, 2008); while other studies documented normal (Shimizu et al., 2003; Jockers-Schrubl et al., 2004; Huang et al., 2006) or even increased circulating BDNF (Gama et al., 2007; Reis et al., 2008). Because of these discrepancies, we decided to perform a systematic review and a meta-analysis of studies measuring serum concentrations of BDNF to elucidate whether or not this neurotrophin is abnormally produced in patients with schizophrenia. Additionally, we were interested in identifying factors that might contribute to the different findings in literature, as to improve the design of future investigations in this field.

2. Methods

2.1 Search strategy

The PUBMED, OVID MEDLINE, PSYCHINFO and EMBASE databases were searched using the following medical subject headings (MeSH): “Brain-Derived Neurotrophic Factor” OR

“BDNF” AND “schizophrenia”. In addition, all reference lists of the selected papers were examined for studies not indexed electronically. The search aimed to find all papers published through January 2011. We used the PRISMA guidelines to carry out this review (Figure 1).

2.2 Inclusion/exclusion criteria for both the systematic review and meta-analysis

Studies had to fulfill the following inclusion criteria :

1. Investigation of serum BDNF levels in patients with schizophrenia and healthy comparison subjects.
2. Mean serum BDNF reported (ng/ml or pg/ml).
3. Clinical characterization of patients with schizophrenia according to DSM-IV, ICD-10 or an equivalent system employed as a diagnostic tool. Study samples including some schizoaffective or schizophreniform subjects were also considered.
4. Published in English.

Exclusion criteria comprised:

1. Samples including non-schizophrenia psychosis or other schizophrenia spectrum disorders.
2. Plasma BDNF levels were measured.
3. Publications describing case reports or case series.
4. Patients or comparison subjects with neurological or medical disorders or substance or alcohol abuse.
5. Comparison subjects screened for psychiatric disorders.

In addition, in the studies exploring the same subject population or part of it, only the publication with the largest sample size was selected. When necessary, study Authors were contacted and asked to supply for missing or incomplete information.

2.3 Data abstraction and quality rating

Each paper was scrutinized by two independent reviewers (D.C. and M.B.) separately, and the following data from the article was obtained: age, gender, education, age at onset, duration of illness, number of hospitalizations, medications used (type, dosage and duration of treatment) and laboratory parameters. Mean serum BDNF levels (expressed in ng/ml) and the methods used for statistical analyses were also extracted from the article. Furthermore, the reviewers rated the quality of each study using a modified version of the quality rating check-list reported on Baiano et al. (2007).

Category 1: subjects

1. Prospective evaluation of patients, use of specific diagnostic criteria and description of demographic data;
2. Prospective evaluation of healthy control subjects, description of demographic data, exclusion of psychiatric and medical illnesses;
3. Presentation of significant variables (e.g. age, gender, age at onset, duration of illness, number of hospitalizations, medications used);

Category 2: methods for sampling and analysis

1. Clear description of laboratory technique and measurements, such in a way to be reproducible;
2. Blindness of investigators to experimental setup;
3. Report of intra and inter-assay reliability;

Category 3: results and conclusions

- Use of appropriate statistical tests;
- Presentation of main results and parameters for statistical significance;
- Consistence of conclusions with the results and discussion of study limits.

Each item was scored 1, 0.5 or 0 if criteria were completely met, partly met or unmet, respectively. This procedure was performed to evaluate the completeness of the available publications and not to criticize the investigations *per se*.

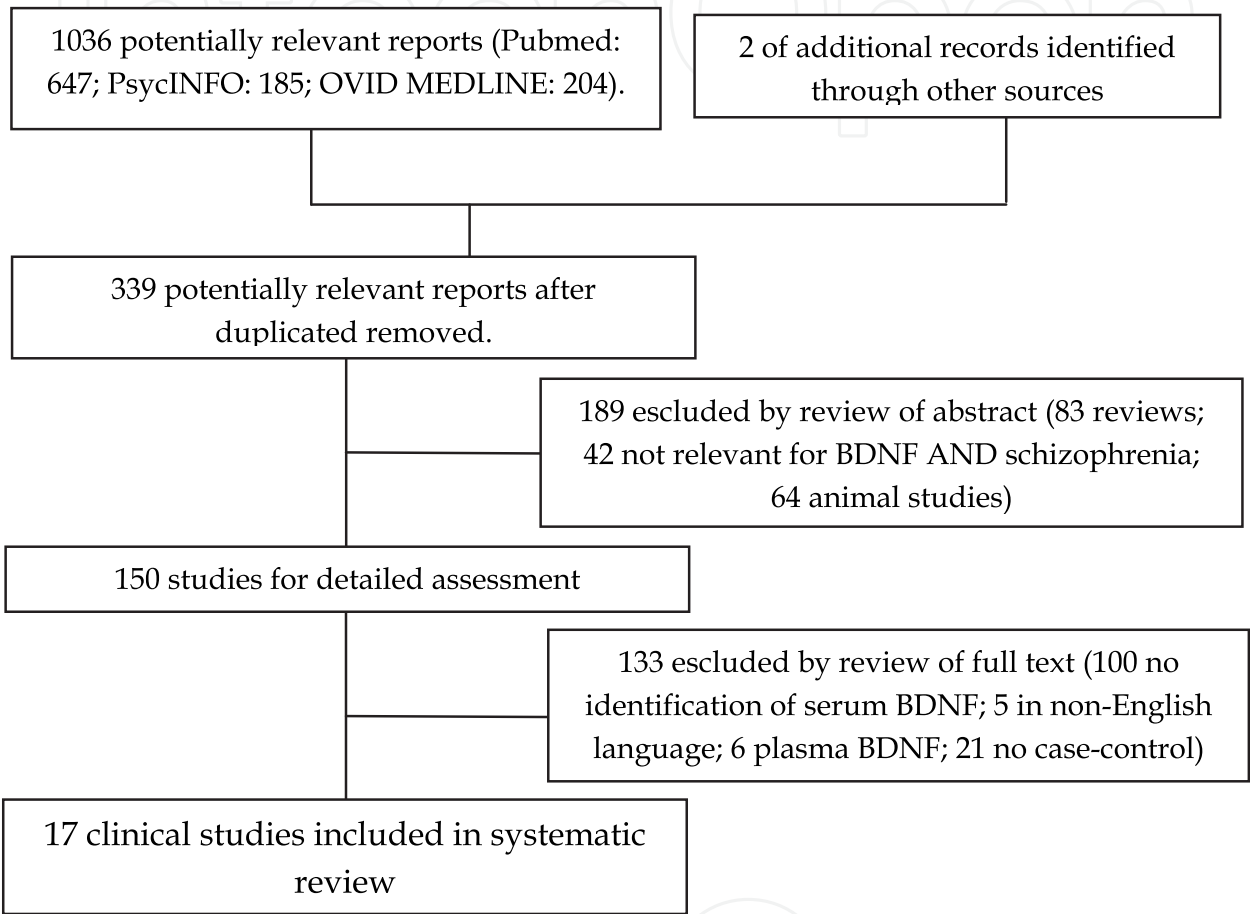


Fig. 1. Flowchart of results of systematic review and meta-analysis search strategy.

2.4 Statistical analysis

The calculations were performed by means of the statistical software package STATA 8.0 (StataCorp LP, Texas). Data were analyzed by using a random effects model (*Metan command*), which typically takes into account the between study variability, leading to wider confidence intervals than those obtained by a fixed effects model. Thus, studies were weighted for the inverse variance, obtaining the DerSimonian-Laird’s effect size (Deeks et al., 2001). Heterogeneity between studies was explored using the Q-test. Since we hypothesized a statistically significant heterogeneity, a meta-regression analysis was planned to assess the effects of selected factors (i.e.: gender distribution, ethnicity, ELISA kit used and average age) on results between studies (*Metareg command*). Publication bias was assessed by Egger’s tests (Egger et al., 1997) (*Metabias command*). All p values were two sided and the cutoff for statistical significance was 0.05.

3. Results

3.1 Systematic review

A total of 334 references were obtained. All the studies found in PUBMED database overlapped with those retrieved using OVID MEDLINE and PSYCHINFO databases. A total of 1036 references were identified. All the studies found in PUBMED database overlapped with those retrieved using OVID MEDLINE, EMBASE, PSYCHINFO lists. Most of them (322) did not meet the inclusion criteria, most analyzing *val66met* BDNF polymorphism, mRNA expression or post-mortem studies.

Thus, 17 were finally considered but 16 were actually included in the systematic review (Carlino et al., 2011; Chen et al., 2009; Gama et al., 2007; Grillo et al., 2007; Huang et al., 2006; Ikeda et al., 2008; Jindal et al., 2010; Jockers-Schröbl et al., 2004; Pirildar et al., 2004; Reis et al., 2008; Rizos et al., 2008; Shimizu et al., 2003; Tan et al., 2005a; Toyooka et al., 2002; Xiu et al., 2009; Zhang et al., 2008). Indeed, as per Authors suggestion, we excluded the study by Zhang et al. (2007) (124 patients and 50 controls) since the patients' sample consistently overlapped with that of the study published by Zhang and co-workers in the 2008 (196 patients and 50 controls).

3.1.1 Findings

Most of the studies (12/16) measuring serum BDNF documented lower concentrations of this neurotrophin in patients with schizophrenia (Carlino et al., 2011; Chen et al., 2009; Grillo et al., 2007; Ikeda et al., 2008; Jindal et al., 2010; Jockers-Schröbl et al., 2004; Pirildar et al., 2004; Rizos et al., 2008; Tan et al., 2005a; Toyooka et al., 2002; Xiu et al., 2009; Zhang et al., 2008); however, in other studies, BDNF concentrations were either increased (Gama et al., 2007; Reis et al., 2008); or normal (Huang et al., 2006; Shimizu et al., 2003) (Table 1).

Five out of the 16 researches investigated gender effects, demonstrating either significantly lower (Xiu et al., 2009) or higher serum BDNF levels in males suffering from schizophrenia (Gama et al., 2007). Conversely, no gender effect emerged in Carlino et al., (2011), Huang et al. (2006) and Rizos et al. (2008) and in all healthy control subjects.

3.1.2 Clinical features of patients

15/16 studies reported on the mean age of the patients with schizophrenia (mean: 37.22 ± 9.48 SD years; range: 22.4-52.3). Nine studies provided data for age of onset of schizophrenia (mean: 25.70 ± 4.86 SD years; range: 19.93-33.8) and 13 for length of illness (mean: 180.13 ± 127.65 SD months; range 8.8-388.8). Six out of 16 papers reported on the mean dosage of antipsychotic medications, expressed as chlorpromazine equivalents (mean: 581.12 ± 219.90 SD; range: 330.4-936.6). In one paper (Zhang et al., 2008), data for other psychopharmacological treatment (lithium, valproic acid) were included, but there were no details about the role of these drugs on serum BDNF levels.

Only Jockers-Schröbl et al. (2004) evaluated the role of substance abuse (cannabis) in serum BDNF levels: the Authors found significantly elevated BDNF serum concentrations (by up to 34%) in patients with chronic cannabis abuse or multiple substance abuse prior to disease onset. Drug-naïve schizophrenic patients without cannabis consumption showed similar results to normal controls and cannabis controls without schizophrenia.

In relation to the source of recruitment, 6/16 studies included only inpatients (Chen et al., 2009; Reis et al., 2008; Rizos et al., 2008; Tan et al., 2005a; Xiu et al., 2009; Zhang et al., 2008), 1/16 included only outpatients (Gama et al., 2007), 3/16 considered both in-patients and

out-patients (Carlino et al., 2011; Huang et al., 2006; Ikeda et al., 2008) and 6/16 publications did not provide data (Grillo et al., 2007; Jindal et al., 2010; Jockers-Schröbl et al., 2004; Pirildar et al., 2004; Shimizu et al., 2003; Toyooka et al., 2002). In our research, we found that Japanese subjects were investigated in three studies (Ikeda et al., 2008; Shimizu et al., 2003; Toyooka et al., 2002), Caucasians in another four studies (Carlino et al., 2011; Jockers-Schröbl et al., 2004; Pirildar et al., 2004; Rizos et al., 2008) and Asians in five studies (Chen et al., 2009; Huang et al., 2006; Tan et al., 2005a; Xiu et al., 2009; Zhang et al., 2008). In four studies, ethnicity was unspecified (Gama et al., 2007; Grillo et al., 2007; Reis et al., 2008; Jindal et al., 2010).

Six studies reported no diagnostic subtypes of schizophrenia (Ikeda et al., 2008; Gama et al., 2007; Jockers-Schröbl et al., 2004; Pirildar et al., 2004; Reis et al., 2008; Rizos et al., 2008; Toyooka et al., 2002) while in seven studies it was assessed the differences in serum BDNF levels among diagnostic subtypes (Chen et al., 2009; Grillo et al., 2007; Huang et al., 2006; Shimizu et al., 2003; Tan et al., 2005a; Xiu et al., 2009; Zhang et al., 2008). Different forms of schizophrenia had no association with BDNF serum levels in 5 papers (Grillo et al., 2007; Shimizu et al., 2003; Tan et al., 2005a; Xiu et al., 2009; Zhang et al., 2008), while Chen et al. (2009) showed significantly higher BDNF levels in paranoid (10.4 ± 4.3 ng/ml) compared to undifferentiated (8.0 ± 3.9 ng/ml) and other combined subtypes (7.5 ± 4.1 ng/ml). Huang et al. (2006) showed that patients with catatonic schizophrenia had lower serum BDNF protein levels than patients with paranoid schizophrenia and residual schizophrenia.

In a second step, phase of illness and use of antipsychotic drugs were considered. We found that four studies enrolled only drug-naïve first-episode patients (Chen et al., 2009; Jindal et al., 2010; Jockers-Schröbl et al., 2004; Rizos et al., 2008), eight studies recruited only chronic, medicated patients (Carlino et al., 2011; Gama et al., 2007; Ikeda et al., 2008; Reis et al., 2008; Tan et al., 2005a; Toyooka et al., 2002; Xiu et al., 2009; Zhang et al., 2008) and two studies included medicated patients with unclear phase of illness (Grillo et al., 2007; Huang et al., 2006). Notably, the study by Pirildar et al. (2004) and Shimizu et al. (2003) investigated both chronically antipsychotic-treated and drug-naïve patients; in particular, in Pirildar et al. (2004) some first episode medicated subjects were included. All the 16 studies excluded patients with a history of neurological disease, physical illness, and alcohol or substance abuse. Clinical data are summarized in Table 2.

3.1.3 Serum BDNF concentrations and laboratory procedures

Among studies, laboratory procedures were comparable with some minor variations. Sera were centrifuged to eliminate the blood clot with a mild centrifugation at 2000, 3000 or 3500 rpm for 5-15min at room temperature or 15°C; then, they were stored frozen at -70/-80°C until used. Serum BDNF concentrations were measured using sandwich ELISA assays (see Table 1 for full detail). Finally, all the studies except one (Gama et al., 2007) reported clearly on mean BDNF concentrations. Specifically, mean serum BDNF values were 14.43 ± 10.24 SD ng/ml (range: 0.098-37.1) for patients and 17.99 ± 13.41 SD ng/ml, (range: 0.12-52.2) for healthy blood donors.

3.1.4 Study quality

The mean total quality scores for the reports were 7.63 ± 1.17 SD (min.:5.5; max.: 9). We correlated total and partial quality scores of studies on serum BDNF with the year of publication, which was significantly positively correlated to total quality score ($r=0.53$) and

study methodology score (Category 2) (r=0.59) but not to study design score (Category 1) (r= -0.20) or study consistency score (Category 3) (r=0.27).

Authors	ELISA kit	Quality of rating (QR)	Control	Schizophrenic patients	
			Serum BDNF (mean ng/ml ± SD)	Serum BDNF (mean ng/ml ± SD)	Medication
Toyoka et al., 2002	Sigma Chemical	6.5	11.4 ± 7.7	6.3 ± 3.4	29=haloperidol, 5=chlorpromazine, 31=levomepromazine, 2=zotepin, 3=bromperidol, 1=risperidone, 9=other
Ikeda et al., 2003	Promega	9	52.2 ± 25.3	37.1 ± 20.4	Typical and atypical (dose not available)
Shimizu et al., 2003 (part I)	Promega	6.5	28.5 ± 9.1	27.9 ± 12.3	----
Shimizu et al., 2003 (part II)		6.5	28.5 ± 9.1	23.8 ± 8.1	
Pirildar et al., 2004 (part I)	Promega	8	26.8 ± 9.3	14.4 ± 2.8	17=risperidone, 2=clozapine, 3=olanzapine
Pirildar et al., 2004 (part II)		8	26.8 ± 9.3	16.3 ± 4.0	
Jockers-Schrübl et al., 2004	Promega	6.5	13.2 ± 5.2	13.1 ± 5.9	----
Tan et al., 2005	BanDing Biomedical	9	9.1 ± 4.3	5.8 ± 2.1	38=clozapine, 19=risperidone, 12=haloperidol, 5=chlorpromazine, 5=perphenazine, 2=others (n = 2)
Huang et al., 2006	Promega	5.5	14.17 ± 6.9	14.2 ± 6.9	----
Grillo et al., 2007	Chemicon	8	0.17 ± 0.0	0.11 ± 0.1	20=Clozapine; 24=typical antipsychotics; 6=chlorpromazine; 15=levomepromazine; 5=haloperidol

Authors	ELISA kit	Quality of rating (QR)	Control	Schizophrenic patients	
			Serum BDNF (mean ng/ml ± SD)	Serum BDNF (mean ng/ml ± SD)	Medication
Zhang et al., 2008	BanDing Biomedical	7.5	9.4 ± 4.4	7.0 ± 3.1	98=clozapine, 36=risperidone, 20=perphenazine, 19=haloperidol, 14=chlorpromazine, 9=fluphenazine, 9=trifluoperazine
Reis et al., 2008	R&D Systems	6	4.31 ± 2.1	7.75 ± 1.9	28=haloperidol, 3=chlorpromazine, 3=levoepromazine, 6=trifluorperazine
Rizos et al., 2008	R&D Systems	7	30.0 ± 8.4	23.9 ± 6.0	----
Xiu et al., 2009	BanDing Biomedical	9	11.9 ± 2.3	9.9 ± 2.0	157=Clozapine, 89=risperidone, 31=haloperidol, 21=chlorpromazine, 26=perphenazine, 27=sulpiride, 13=other
Chen et al., 2009	BanDing Biomedical	8.5	12.1±2.2	9.0±4.2	----
Jindal et al., 2010	Promega	9	116.78±38.42	97.58±31.41	----
Carlino et al., 2011	Promega	9	26.5 ± 4.22	25.3 ± 3.71	4=haloperidol, 2=zuclopenthixol, 2=haloperidol decanoate, 10= olanzapine, 6=risperidone, 8=quetiapine, 1=olanzapine +zuclopenthixol , 2=olanzapine +haloperidol, 2=quetiapine +haloperidol,2= quetiapine +zuclopenthixol, 3=risperidone+haloperidol

Table 1. Methodological aspects of the studies measuring serum BDNF in schizophrenia. *

3.1.5 Meta-analysis

Fifteen out of the 16 publications considered for the systematic review were used for the meta-analysis (Carlino et al., 2011; Chen et al., 2009; Grillo et al., 2007; Huang et al., 2006; Ikeda et al., 2008; Jindal et al., 2010; Jockers-Schröbl et al., 2004; Pirildar et al., 2004; Reis et al., 2008; Rizos et al., 2008; Shimizu et al., 2003; Tan et al., 2005a; Toyooka et al., 2002; Xiu et al., 2009; Zhang et al., 2008). The study by Gama et al., (2007) was eliminated, as it was the only one to report serum BDNF in pg/ μ g of total protein while in all other studies serum BDNF concentration was given in ng or pg/ml serum and therefore, no comparison between the Gama's and the other studies was possible. Since the studies by Shimizu et al., (2003) and Pirildar et al., (2004) reported on separate data for both medicated and unmedicated patients, we performed calculations considering patients' subgroups as follows: Shimizu et al., 2003 part I and Pirildar et al., 2004 part I = medicated patients; Shimizu et al., 2003 part II and Pirildar et al., 2004 part II = unmedicated patients. Therefore, we carried out calculations on 17 samples of patients.

Authors	Stages of disease	Ethnicity *	Control			Schizophrenic patients			
			N	Age (mean \pm SD)	M/F	N	Age (mean \pm SD)	M/F	Illness duration (mean-months \pm SD)
Toyoka et al., 2002	Chronic	JPT	35	45.6 \pm 11.3	14/21	34	48.6 \pm 14.0	17/17	25 \pm 12.3
Ikeda et al., 2003	Chronic	JPT	87	39.8 \pm 10.7	47/40	74	41.9 \pm 11.1	39/35	19.6 \pm 11.2
Shimizu et al.,2003 (part I)	Chronic	JPT	40	36.5 \pm 11.3	20/20	25	36.0 \pm 13.2	13/12	Med scz: 14.1 \pm 9.87; FEP: 1.09 \pm 1.36
Shimizu et al.,2003 (part II)	First episode/ drug naïve	JPT	40	36.5 \pm 10.7	20/20	15	34.7 \pm 16.0	7/8	
Pirildar et al., 2004 (part I)	Chronic	CEU	22	25.7 \pm 5.8	7/15	12	29.8 \pm 9.3	5/7	15.2 \pm 13.04
Pirildar et al., 2004 (part II)	First episode/ drug naïve	CEU	22	25.7 \pm 5.8	7/15	10	25.1 \pm 9.1	2/8	
Jockers-Schröbl et al., 2004	First episode/ drug naïve	CEU	61	32.3	28/33	102	33.3	50/52	----
Tan et al., 2005	Chronic	CHB	45	45.6 \pm 6.3	34/11	125	18.3 \pm 6.3	93/32	22.6 \pm 7.7
Huang et al., 2006	Chronic	CHB	96	29.1 \pm 10.0	36/60	126	34.0 \pm 10.0	72/54	6.0 \pm 5.0
Grillo et al., 2007	Chronic	YRI/CEU (ratio not specified)	25	34.1 \pm 7.2	12/13	44	35.5 \pm 7.2	19/25	

Authors	Stages of disease	Ethnicity *	Control			Schizophrenic patients			
			N	Age (mean ± SD)	M/F	N	Age (mean ± SD)	M/F	Illness duration (mean-months ± SD)
Zhang et al., 2008	Chronic	CHB	50	----	34/16	196	----	130/66	22 ± 7
Reis et al., 2008	Chronic	YRI/CEU (ratio not specified)	20	----	20/0	40	52.3 ± 9.8	40/0	32.4 ± 9.2
Rizos et al., 2008	First episode/ drug naïve	CEU	15	26.6 ± 5.8	6/9	14	25.4 ± 5.8	10/4	----
Xiu et al., 2009	Chronic	CHB	323	50.9 ± 9.2	228/95	364	51.3 ± 9.2	281/83	27.0 ± 10.1
Chen et al., 2009	First episode/ drug naïve	CHB	90	29.9 ± 9.8	49/41	88	29.2 ± 9.6	47/41	23.4 ± 19.1
Jindal et al., 2010	First episode/ drug naïve	CEU	41	22.31 ± 5.67	25/16	24	22.4 ± 5.47	17/10	----
Carlino et al., 2011	Chronic	CEU	40	46.78 ± 10.79	20/20	40	49.23 ± 9.03	20/20	23.05 ± 10.99

Table 2. Clinical characteristics of studies included in the meta-analysis. International HapMap Project: YRI: Yoruba in Ibadan, Nigeria; JPT: Japanese in Tokyo; CHB: Han Chinese in Beijing, China; CEU: CEPH (Utah residents with ancestry from Northern and Western Europe).

Raw total serum BDNF levels (ng/ml) were used to calculate the related effect sizes. The overall estimate of SMD (*standardized mean differences*) in serum BDNF levels between patients with schizophrenia and healthy controls was significant ($z=4.14$; $p<0.001$) but considerable heterogeneity emerged from publications ($Q=139.15$; $d.f.=16$; $p<0.001$; $\tau^2=0.2826$) (Figure 2). Therefore, we regressed the SMD against potential sources of heterogeneity (i.e.: gender, age, ethnicity and ELISA kit used). This analysis demonstrated a significant association of BDNF levels with all these variables (age: $z=15.28$; gender: $z=10.92$ for males; $z=4.60$ for females; ethnicity: $Z=9.37$ and ELISA kit: $z=8.55$; $p<0.001$). Moreover, to determine if this systematic review and meta-analyses was subjected to publication bias (i.e. the presence of asymmetrical collection of data due to the missing of studies reporting negative results, or to the tendency of small studies to show greater effects than larger studies), we carried out the Egger’s weighted regression and evidence of significant publication bias was found ($p<0.001$). Subsequently, the eleven studies investigating chronic, medicated patients with schizophrenia were considered (Carlino et al., 2011; Grillo et al., 2007; Huang et al., 2006; Ikeda et al., 2008; Pirildar et al., 2004 part I; Reis et al, 2008; Shimizu et al., 2003 part I; Tan et al., 2005a; Toyooka et al., 2002; Xiu et al., 2009; Zhang et al., 2008). Significant heterogeneity was found ($Q=120.85$, $d.f.=10$, $p<0.001$, $\tau^2=0.3545$) and patients and healthy control subjects differed for serum BDNF levels, as demonstrated by the SMD test ($z=2.69$; $p=0.007$) (Figure 3).

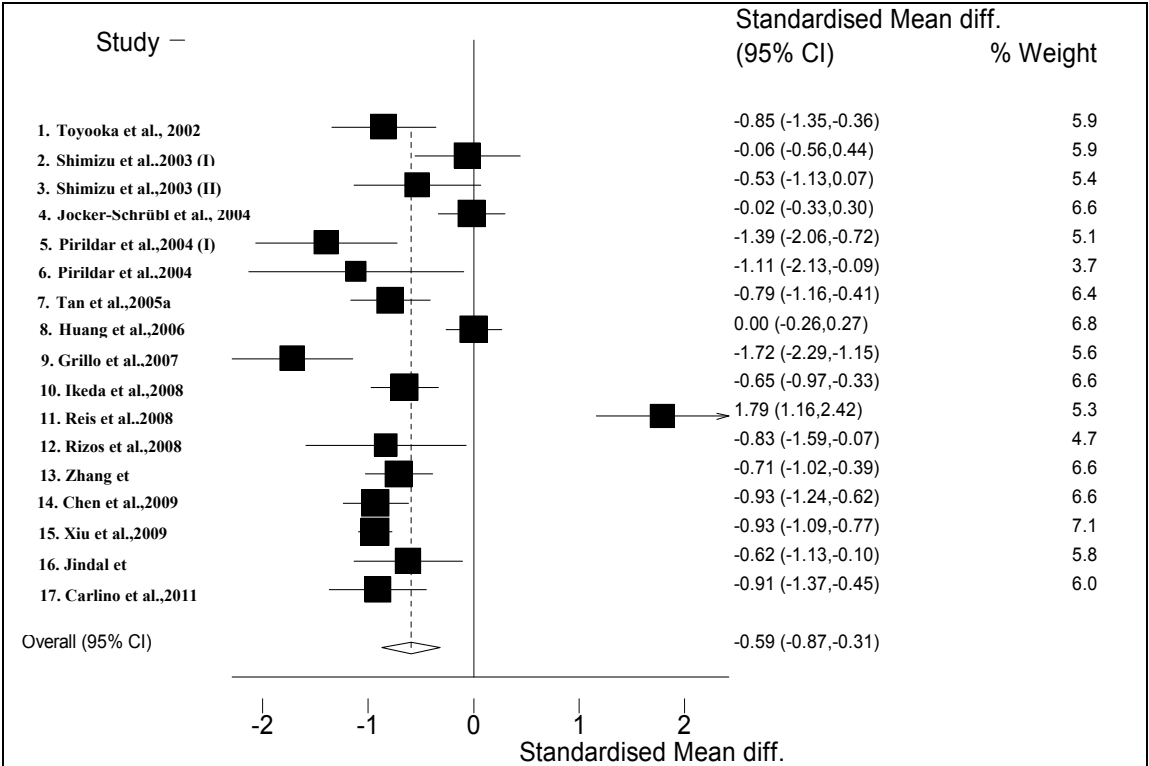


Fig. 2. Forrest plot depicting the meta-analysis of serum BDNF levels in patients with schizophrenia.

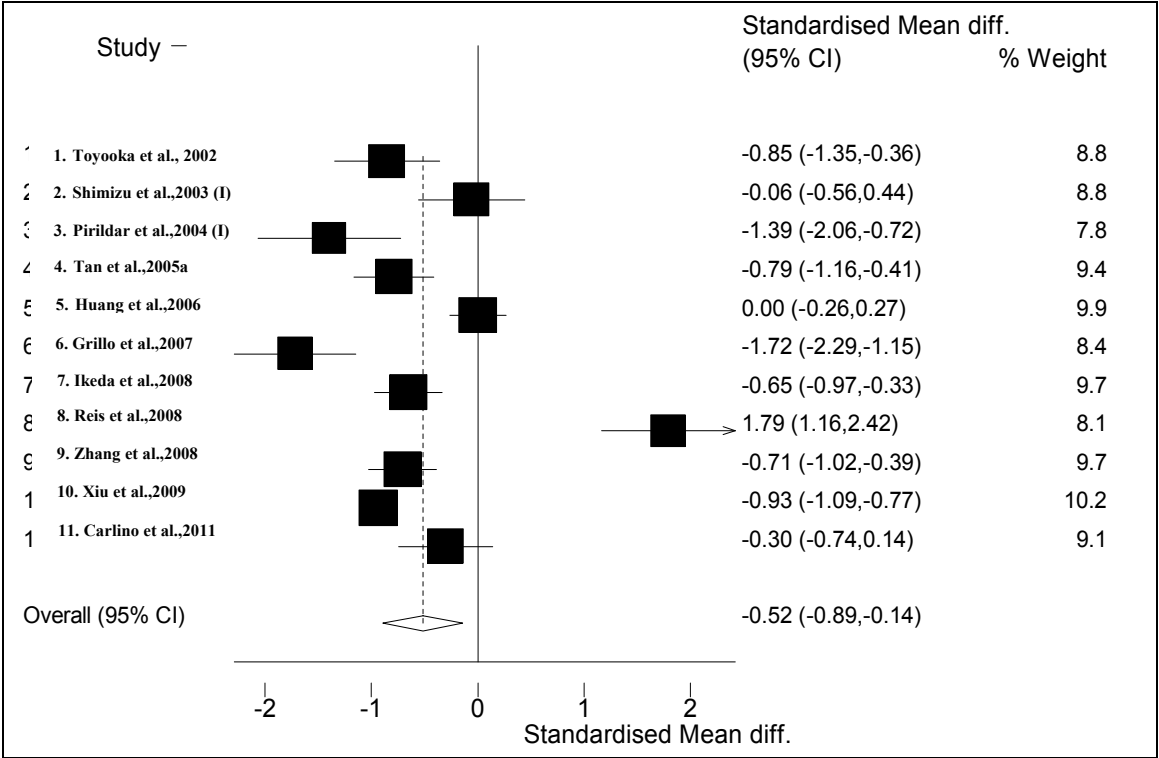


Fig. 3. Forrest plot presenting the meta-analysis of serum BDNF in chronic medicated patients with schizophrenia.

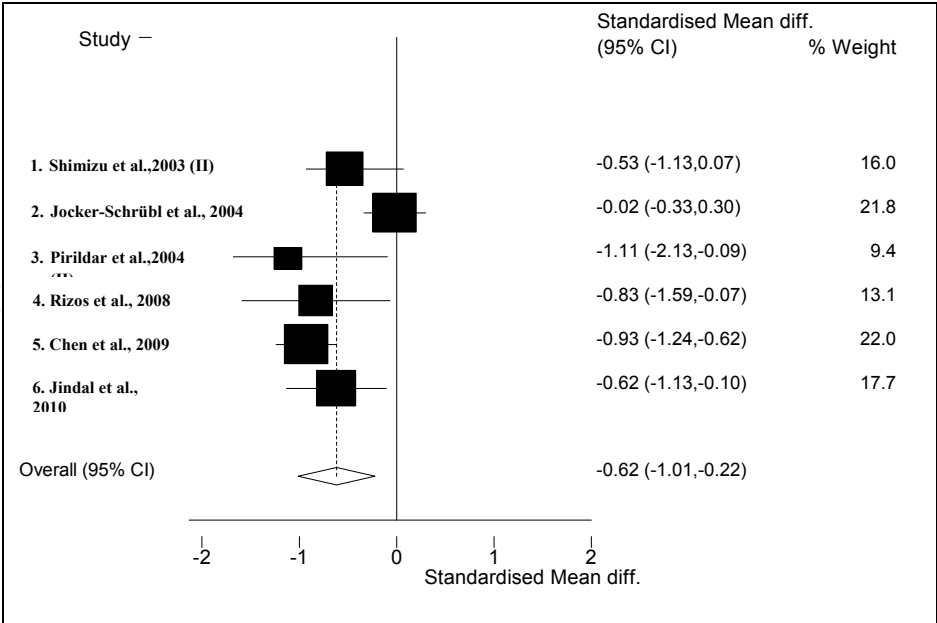


Fig. 4. Forrest plot presenting the meta-analysis of serum BDNF in unmedicated patients with schizophrenia.

The meta-regression analysis showed that age ($z=13.89$), gender ($z=11.09$ for males; $z=7.36$ for females), ethnicity ($z=6.76$), type of ELISA kit ($z=6.67$), chlorpromazine equivalents' medication dosage ($z=5.97$) and duration of illness ($z=7.03$) may all explain heterogeneity ($p<0.001$). Similar results were obtained by meta-analyzing the six studies including first-episode unmedicated patients (Chen et al., 2009; Jindal et al., 2010; Pirildar et al., 2004; Rizos et al., 2008; Shimizu et al., 2003 part II) (Figure 4). Indeed, we found that both the Q test for heterogeneity ($Q=18.30$; $d.f=5$; $p=0.003$; $\tau^2=0.1595$) and Dersimonian and Laird pooled effect size ($z=3.06$, $p=0.002$) were significant. As previously demonstrated, heterogeneity may be due to age ($z=15.33$), gender ($z=4.55$ for males; $z=4.84$ for females), ethnicity ($z=5.47$), type of ELISA kit ($z=4.45$).

4. Conclusion

Our systematic review and meta-analysis showed that lower serum BDNF levels were detected in patients with schizophrenia in comparison to healthy controls in most even if not in all studies. Interestingly, reduced serum BDNF levels were found both in drug-naïve first episode and chronic medicated schizophrenia patients, as also found in studies investigating plasma BDNF concentrations (Buckely et al., 2007; Palomino et al., 2006; Tan et al., 2005b). These findings show that reduced serum BDNF levels are associated with schizophrenia but also suggest that serum BDNF is not a crucial biological marker of the clinical state in schizophrenia or a marker of antipsychotic medication efficacy, in agreement with a recent meta-analysis (Green et al., 2010).

The serum BDNF concentration in healthy populations, varied from a minimum of 0.17 ng/ml (Grillo et al., 2007) to a maximum of 52.2 ng/ml (Ikeda et al., 2003), the mean value among the thirteen paper analysed was 16.2 ng/ml (SD=14.59). Although we observed variability between studies using the same commercial ELISA, differences in serum BDNF concentration appeared mainly due to the different kit used. For example the three studies

which used the kit purchased from BanDing Biomed reported values of serum BDNF in Chinese healthy donors of 11.9 ± 2.3 ng/ml (Xiu et al., 2009); 9.4 ± 4.4 ng/ml (Zhang et al., 2008); 9.1 ± 4.3 ng/ml (Tan et al., 2005) while higher levels of serum BDNF were detected with the kit from Promega in healthy donors from Japan, 28.5 ± 9.1 ng/ml (Shimizu et al., 2003); Turkey 26.8 ± 9.3 ng/ml (Pirildar et al., 2004) and Taiwan 14.17 ± 6.9 ng/ml (Huang et al., 2006). Finally, two studies using the R&D System ELISA assay showed very distant results because Rizos et al. (2008) detected 30.0 ± 8.4 ng/ml of serum BDNF in healthy controls from Greece while Reis et al., (2008) in Brazil, found 4.31 ± 2.1 ng/ml. Two other studies from Brazil also showed particularly low levels using the assay from another company (Chemicon), i.e. 0.19 ± 0.1 ng/ml (Gama et al., 2007) and 0.17 ± 0.0 ng/ml (Grillo et al., 2007). It is possible that this finding might reflect reduced amounts of serum BDNF in the Brazilian population. Another interpretation suggests a very low sensitivity of the ELISA kit from Chemicon. In conclusion, the most likely range of concentrations of serum BDNF in the World healthy population is 9-30 ng/ml with some possible specific regional variations.

However, the great heterogeneity between studies and the presence of a publication bias may limit the interpretation of these results. Firstly, the phenotypic complexity, together with the multifarious nature of the so-called “schizophrenic psychoses”, limits our ability to form a simple and logical, biologically-based hypothesis for the disease group. Secondly, all studies used ELISA assays that have different sensitivity and cannot distinguish between the three different protein forms of BDNF consisting in the precursor pro-BDNF (of 32 KDa) and its two proteolytic products mature BDNF (mBDNF of 14KDa) and truncated BDNF (truncBDNF of 28 KDa). Since pro-BDNF and mBDNF elicit opposing actions on synaptic plasticity and cell survival, their distinction could be essential to determine the role of BDNF in specific aspects of schizophrenia’s neurobiology.

4.1 The role of proBDNF in patients with schizophrenia

BDNF is initially synthesized as a 32 KDa precursor protein (prepro-BDNF) in endoplasmic reticulum, and then processed into two isoforms (as the truncated-BDNF 28 KDa and mature 14 kDa BDNF) by two different proteolytic cleavages. Mature BDNF (mBDNF) is generated either intracellularly in the trans-Golgi by furin (Mowla et al., 2001, Matsumoto et al., 2008), or extracellularly by plasmin or matrixmetalloprotease-7 (Lee et al., 2001, Yang et al. 2009; Nagappan et al., 2009). Truncated-BDNF is cleaved by the Membrane-Bound Transcription Factor Site-1 protease (MBTFS-1), also identified as Subtilisin/kexin-isozyme 1 (Seidah et al., 1999). This isoform is not further processed into mBDNF and its function has not been elucidated yet.

According to the “Ying and Yang” hypothesis (Lu et al., 2005), both mBDNF and proBDNF have particular neurobiological properties. In particular, proBDNF regulate neuronal survival (Teng et al., 2005; Koshimizu et al., 2009; Woo et al., 2005) and boosts synaptic pruning whereas mBDNF improves the differentiation of new neurons. Also, the conversion of proBDNF into mBDNF seems to be decisive for signal transmission and synaptic plasticity. Indeed, mBDNF and the Tissue Plasminogen Activator (TPA) but not proBDNF are essential in late-phase long-term potentiation (L-LTP) and long-term memory (Pang et al., 2004). These results underscore that a wrong matching of the proBDNF/mBDNF ratio may alter neuroplastic mechanisms, corresponding to the neurobiological substrate of impaired cognitive performance.

An increasing number of postmortem researches have been carried out to measure the expression of proBDNF and mBDNF isoforms in animal models and in healthy human volunteers or subjects affected by neuropsychiatric disorders. Reduced mBDNF levels were found in three studies (Karege et al., 2005; Weickert et al., 2003; Wong et al., 2010), particularly in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia compared to healthy controls. Weickert et al. (2003) found that mBDNF protein levels were not associated with post-mortem interval (PMI), tissue pH, age, or storage time of the serum. There were no significant main influences of gender or brain hemisphere, nor significant correlations between diagnosis and gender or diagnosis and brain hemisphere. On the other hand, Chen et al. (2001) showed that there was no significant variation for mBDNF among patients with schizophrenia and those with a diagnosis of affective disorders (unipolar and bipolar disorders) and Dunham et al., (2009) detected no difference for preproBDNF (35KDa) between patients with schizophrenia and those with unipolar depression and bipolar disorder. In contrast, Wong et al. (2010) found reduced truncated BDNF and preproBDNF proteins in the DLPFC of patients with schizophrenia, even if the reduction in preproBDNF protein did not achieve statistical significance.

In a previous study (Carlino et al., 2011), we provided evidence of variation in serum levels of different BDNF isoforms in patients with chronic schizophrenia. Particularly, we showed that reduced levels of serum truncated-BDNF/total BDNF ratio correlate with worst PANSS negative and positive symptoms and poorer neurocognitive functions. Instead, measurement of total serum BDNF levels resulted scarcely useful, even if we found a small decline in the whole population of schizophrenic patients. We further highlighted that when using a cut-off at the mean value of the healthy group + 2SD, the measurement of serum truncated-BDNF represents a useful empirical test to recognize schizophrenic patients with high cognitive impairment, with sensitivity = 67.5%, Specificity = 97.5%, PPV = 96.4% and NPV = 75%.

Regulated proteolysis of one inactive precursor to make active peptides and proteins is a general biological mechanism to generate different products from a single gene. Mammalian pro-BDNF precursor is processed to generate truncated-BDNF 28 KDa or mature 14 kDa BDNF by two dissimilar proteolytic cleavages. Mature BDNF is created intracellularly by furin (Mowla et al., 2001), or extracellularly, by plasmin or matrixmetalloprotease-7 (Lee et al., 2001), whereas truncated-BDNF is generated by a specific Ca^{2+} -dependent serine proteinase known as Membrane-bound transcription factor site-1 protease (MBTFS-1), also identified as Subtilisin/Kexin-Isozyme 1 (SKI-1) (Seidah et al., 1999); it is not further processed into the mature 14 kDa BDNF form representing a final proteolytic product whose role is ambiguous. Recent findings have established that mature and pro-BDNF elicit opposite biological functions (Teng et al., 2005; Woo et al., 2005), leading to the hypothesis that from an incorrect balancing of the diverse isoforms may origin a pathological consequence. In recent times, Koshimizu et al. (2009) pointed out that overexpression of pro-BDNF leads to apoptosis of cultured cerebellar granule neurons and produce a striking decrease in the number of cholinergic fibers of basal forebrain neurons and hippocampal dendritic spines, without disturbing the survival of these neurons. Blockade of activation of p75 receptor did not permit spine number to fall. Importantly, the pro-BDNF preparation used in this paper contained a large amount of truncated-BDNF, although at a much lesser extent than pro-BDNF. It is therefore possible that truncated-BDNF may have a similar outcome than pro-BDNF through activation of the same signalling pathways. Alternatively,

truncated-BDNF may be an inactive variety of pro-BDNF or operate as a quencher of pro-BDNF by producing inactive heterodimers. The latter possibility reminds the supposed function for truncated-TrkB. Hence, a clear decrease in truncated-BDNF may direct to pathologically amplified signalling of pro-BDNF. Further studies will be necessary to clarify the biological characteristics of truncated-BDNF.

Chronic patients with schizophrenia are often characterized to suffer progressive significant intellectual decline (Heinrichs, 2006). In our study, schizophrenic patients with reduced truncated-BDNF had worse efficiency in all neurocognitive tests in relationship to the other patients with normal levels of truncated-BDNF, although the correlation between Trail Making Test Part A score and truncated-BDNF abundance do not reach the statistically significance. Our results further enlarge a recent research telling that evaluation of total serum BDNF may be useful to predict for a good outcome in neurocognitive enhancement sessions in schizophrenic patients (Vinogradov et al., 2009). Importantly, we also underline that four healthy subjects with low truncated-BDNF had poor scores in Trail Making Test B and Symbol Digit Coding attention test. So we can hypothesize that schizophrenic patients with low serum truncated-BDNF and worse cognitive functioning are likely to be more resistant to a non-psychopharmacological neurocognitive training.

On the basis of these findings, we sharpen the role of evaluation of serum BDNF as an empirical system to estimate cognitive defects related to proBDNF processing as a potential biological system basic in the pathophysiology of schizophrenia.

4.2 The role of ethnic differences in serum BDNF levels in patients with schizophrenia

An element of heterogeneity that emerges from this meta-analysis is represented by the ethnic differences amongst the samples. In this context it is of great interest to note that there are divergent findings of the positive or negative associations between BDNF *val66met* polymorphism and schizophrenia, especially in Caucasian and Asian participants. These differences may partially explain the differences in serum BDDNF levels among papers. Studies in *in vitro* and in animal models have shown that Met allele alters both sorting and secretion of proBDNF, such that less regulated (activity dependent) secretion is likely to occur in carriers of at least one Met allele. Several genetic associational studies have shown that SNPs in BDNF are associated with schizophrenia (Nanko et al., 2003; Szekeres et al., 2003), and a meta-analysis study also illustrated an association between C270T and schizophrenia (Zintzaras, 2007), but not between Val66Met and schizophrenia (Kanazawa et al., 2007; Naoe et al., 2007; Xu et al., 2007; Zintzaras, 2007).

Great differences in the allelic frequencies for the BDNF Val66Met polymorphism between populations of different ethnic origins have been reported in public databases (<http://www.hapmap.org>) for the same populations (Tables 3 and 4). In Caucasian subjects, the frequency of the Met allele is 25–32%, whereas in Asian peoples the Met allele is more frequent, around 40–50% (Pivac et al., 2009; Verhagen et al., 2010). These variations among different ethnic groups in the allelic frequencies of the BDNF polymorphism may be caused by either the natural selection of an advantageous allele by unknown environmental issues or through a founder effect.

However, we advise prudence in the analysis of these facts, also because despite this obvious difference in outcomes of schizophrenia across ethnicities, cross-cultural research in psychiatry focuses on similarities rather than differences. For example, subtypes of schizophrenia may have different prevalence across countries: in the International Pilot

Study of Schizophrenia (1973) and the Determinants of Outcome of Severe Mental Disorders study (1992), catatonia was identified in 10% of cases in developing countries respect to less than 1% in developed countries. Hebephrenia was found in 13% of cases in developed countries and 4% in developing countries. Currently, we have not sufficient data about the role of diagnostic subtypes and serum BDNF levels or BDNF polymorphisms.

Genotype - Population descriptors	Genotype frequencies
G/G - YRI	0.683
G/G - JPT	0.190
G/G - CHB	0.488
G/G - CEU	1.000
A/G- YRI	0.283
A/G- JPT	0.357
A/G- CHB	0.349
A/G- CEU	n.a.
A/A- YRI	0.033
A/A- JPT	0.452
A/A- CHB	0.163
A/A- CEU	0

Table 3. YRI: Yoruba in Ibadan, Nigeria; JPT: Japanese in Tokyo, Japan; CHB: Han Chinese in Beijing, China; CEU: CEPH (Utah residents with ancestry from northern and western Europe). G/G = Met/Met; A/G =Val/Met; A/A = Val/Val.

Allele - Population descriptors	Allele frequencies
G- YRI	0.825
G- JPT	0.369
G- CHB	0.663
G- CEU	1.000
A- YRI	0.175
A - JPT	0.631
A- CHB	0.337
A- CEU	0

Table 4. YRI: Yoruba in Ibadan, Nigeria; JPT: Japanese in Tokyo, Japan; CHB: Han Chinese in Beijing, China; CEU: CEPH (Utah residents with ancestry from northern and western Europe).

Another diagnostic caveats regards the Caucasian studies that often investigated not only patients with schizophrenia, but also subjects with schizophrenia spectrum disorders such as schizophreniform disorder or schizoaffective disorder, while Asian and other studies investigated only patients with schizophrenia. This difference in methodology might also have contributed to the inconsistent findings between the Caucasian and the Asian studies. The substantial variation in the Val66Met frequencies between Asian and Caucasian samples indicates that ethnicity may be of importance in the issue, because if the association among Caucasians reflects linkage disequilibrium with another gene variant, the extent of linkage may vary between populations. A recent study focused on the complex

microsatellite polymorphism BDNF-LCPR located ~1.0 kbp upstream of the translation initiation site of BDNF (Okada et al., 2006); this polymorphism contained 23 novel allelic variants, including four major alleles (A1–A4). Kawashima et al. (2009) consider that if BDNF is indeed associated with schizophrenia, the A1 allele in BDNF-LCPR would be a hopefully useful marker in the Japanese population.

Also, we must not forget the interchange between genetic and environmental issues, that may essentially vary for men and women. In this regard, it would be interesting to evaluate if gender-related epistatic effects pertaining to the *Val66Met* polymorphism subsist. Literature data showed that gender differences in schizophrenia reproduce divergences in neurodevelopmental mechanisms and social influences on illness risk and course. Men have poorer premorbid functioning and have worse negative and less depressive manifestations than women. Substance abuse is more frequent in male. Results of gender variations in brain morphology (e.g. hippocampal volume) are conflicting but refer to matter of sexual dimorphism, meaning that the same elements are significant to explain sex disparities in both normal neurodevelopment and those in relationship with schizophrenia.

Another factor to consider is the epigenetic influence. “Epigenetic” refers to the covalent modifications of chromatin. Epigenetic machinery not only is responsible for lasting differences in gene activity in the CNS but also controls gene expression necessary for cognition. Thus, the likelihood of an epigenetic involvement in schizophrenia is an interesting hypothesis. In fact, epidemiological studies have identified several environmental risk factors for schizophrenia, counting marijuana consumption and obstetric complications. A recent study by Nicodemus and colleagues (2008) showed a significant association between four candidate genes for schizophrenia which are likely to have a role in hypoxic situations, including BDNF detecting significant evidence for gene x environment interaction in schizophrenic patients with or without obstetric complications. Recently, several studies underline that DNA methylation contributing to ongoing regulation of BDNF transcription in the CNS to control synaptic plasticity and memory mechanism (for e review, see Roth et al., 2009a). In addition, BDNF DNA methylation has also been found to play a part in altered gene expression in response to environmental pressure, such as social experiences (Roth et al., 2009). Indeed, stressful social experiences early in life have long-lasting consequences such as increased anxiety, drug-seeking behavior, cognitive impairment, and altered affiliative behaviours (Branchi et al., 2004; Fumagalli et al., 2007; Lippmann et al., 2007). Finally, it was recently revealed that social experiences early during the first postnatal week generate lasting changes in DNA methylation in BDNF gene in relationship with reduction of BDNF gene expression in the adult prefrontal cortex (Roth et al., 2009b).

Overall, the available data suggest that DNA methylation may indeed be an epigenetic mechanism that contributes to the aberrant regulation of genes associated with schizophrenia. The hard work to recognize vulnerability genes for multifactorial disorders such as schizophrenia, has inspired the development of alternative methodologies. Since genetic heterogeneity has been a major dilemma in complex disorders, investigators have attempted to increase homogeneity in their samples. Recently, alternative phenotypic definitions have been defined that might be more closely linked to biological pathway (*endophenotypes*), for example sensory gating deficits or working memory dysfunction (Gottesman and Gould, 2003).

Another advance to decrease basic genetic complexity is the utilization of genetic isolates. Isolated populations originated from a small number of founder couples. Throughout history, many populations, counting isolated as well as outbred populations, undergo

alternating era of adversities (e.g. war, epidemics, or famine) with period characterized by rapid growth of the population. Due to increased inbreeding and genetic drift in isolates, certain alleles will be present more frequently in the population, while others are lost, increasing genetic homogeneity. Additionally, due to geographic, cultural, or religious barriers, isolated populations did not experience a large degree of admixture with adjacent peoples for many generations, ensuing in a relatively small gene pool ("founder effect").

So the recognition of a gene or allele that clinically and/or genetically is not as important in outbred populations as in isolated populations might untangle molecular pathways and find out new candidate genes, which might have a higher involvement on illness risk in general. Several studies highlight susceptibility loci for schizophrenia in isolated populations (Venken et al., 2007).

4.3 Future research proposals

The hypothesis that relapse could be predicted by low neurotrophin levels is consistent with the neurobiology of relapse and with preliminary data in first episode psychosis patients (Parikh et al., 2003). Therefore, large populations of high-risk subjects or untreated first episode patients need to be longitudinally investigated to improve the statistical importance of the analysis (Pantelis et al., 2003). In fact, in the absence of a neuroleptic naïve cohort followed longitudinally to evaluate pattern of neurotrophins over time, it is difficult to determine whether any relationship between relapse and low neurotrophins would be due to an underlying neurobiological vulnerability to relapse, an inadequate therapeutic response to antipsychotics, or inadequate antipsychotic exposure due to medication noncompliance. In the first part of the meta-analysis, serum BDNF levels were shown to be reduced in patients with schizophrenia even if the difference was moderately significant ($p < 0.05$). However, considerable statistical heterogeneity was detected between studies. In the second part of the meta-analysis, we found that serum BDNF levels in patients with drug free/first episode psychosis were significantly lower in patients compared to healthy control subjects, but we could not detect any significant alteration in serum BDNF levels in patients with chronic schizophrenia. In both cases, a high heterogeneity was between the studies was highlighted and it is still unclear whether the reduction in serum BDNF levels observed in drug naïve/first episode patients with schizophrenia is due more to antipsychotic treatment or toxic effect of psychosis in itself. Therefore, future biochemical studies should longitudinally investigate larger samples of high-risk individuals, drug free first-episode patients and unaffected family members. Such populations are crucial to systematically examine whether serum BDNF levels changes are already present before the appearance of symptoms, or whether they develop afterwards, as a result of the course of illness. Such biochemical studies, should be crossed with MRI, genetic and metabolism investigations data, in order to further investigate whether serum BDNF levels represent an indicator of vulnerability to the disease and to better understand the functional expression of serum BDNF levels abnormalities in schizophrenia.

5. References

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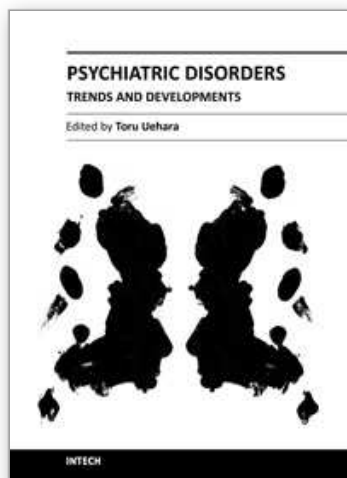
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Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, severe and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning is in some cases tragic. Aside from knowing the physical organic factors, such as infections, endocrinal illnesses or head injuries, the aetiology of psychiatric disorders has remained a mystery. However, recent advances in psychiatry and neuroscience have been successful in discovering subsequent pathophysiology and reaching associated bio-psycho-social factors. This book consists of recent trends and developments in psychiatry from all over the world, presented in the form of multifarious and comprehensive articles. The first two sections of the book are reserved for articles on schizophrenia and depression, two major illnesses present in this field. The third section of the book is reserved for addiction psychiatry, related not only to socio-cultural but also biological alterations. The last section of the book, titled Biological Neuropsychiatry, consists of three topics - updated molecular biology, fundamental neuroscience and clinical neuropsychiatric conditions. Doubtlessly, this book will be fruitful for future developments and collaboration in world psychiatry.

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