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WFSBP CONSENSUS PAPER

Consensus paper of the WFSBP Task Force on Genetics: Genetics, epigenetics and gene expression markers of major depressive disorder and antidepressant response

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ABSTRACT

Major depressive disorder (MDD) is a heritable disease with a heavy personal and socio-economic burden. Antidepressants of different classes are prescribed to treat MDD, but reliable and reproducible markers of efficacy are not available for clinical use. Further complicating treatment, the diagnosis of MDD is not guided by objective criteria, resulting in the risk of under- or overtreatment. A number of markers of MDD and antidepressant response have been investigated at the genetic, epigenetic, gene expression and protein levels. Polymorphisms in genes involved in antidepressant metabolism (cytochrome P450 isoenzymes), antidepressant transport (*ABCB1*), glucocorticoid signalling (*FKBP5*) and serotonin neurotransmission (*SLC6A4* and *HTR2A*) were among those included in the first pharmacogenetic assays that have been tested for clinical applicability. The results of these investigations were encouraging when examining patient-outcome improvement. Furthermore, a nine-serum biomarker panel (including *BDNF*, cortisol and soluble TNF-α receptor type II) showed good sensitivity and specificity in differentiating between MDD and healthy controls. These first diagnostic and response-predictive tests for MDD provided a source of optimism for future clinical applications. However, such findings should be considered very carefully because their benefit/cost ratio and clinical indications were not clearly demonstrated. Future tests may include combinations of different types of biomarkers and be specific for MDD subtypes or pathological dimensions.

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1. Introduction

Major depressive disorder (MDD) was among the five leading diseases contributing to DALYs in 2010 in the USA, after cardiovascular diseases and lung cancer (Murray et al. 2013). The disorder also carries with it a substantial increase in suicide risk (Bradvik et al. 2008), a quality of life comparable to that of severe physical disorders such as arthritis and heart disease (Buist-Bouwman et al. 2006) and significant health expenditures, with direct costs alone amounting to 42 billion dollars in Europe (Sobocki et al. 2006).

Despite the demonstrated efficacy of antidepressant medications, high inter-individual variability is observed in both response and side-effect occurrence and the lack of reliable markers of these outcomes contributes to unsatisfactory treatment effectiveness, poor treatment adherence and early treatment discontinuation (Fabbri et al. 2013a). Furthermore, few studies include or adjust for placebo response, which has been shown to account for 67.6% of the efficacy observed in antidepressant treatment (Rief et al. 2009). Placebo response is a major concern for drug trials, as well as for biomarker investigations, and likely has a significant genetic component (Walsh et al. 2002; Tiwari et al. 2013; Holmes et al. 2016). Importantly, objective criteria are not available to support the diagnosis of MDD based on clinical criteria only, resulting in the risk of clinician-dependent variability in terms of both diagnosis type and severity. Indeed, two well-known scenarios are observed in clinical settings: the diagnosis conflates adaptive sadness reactions with pathological states of depressed mood, resulting in overdiagnosis and overtreatment; on the other hand, underdiagnosis and undertreatment may lead to a severe, chronic, recurrent or treatment-resistant course (Lorenzo-Luaces 2015).

Research has been oriented toward the identification of biomarkers of MDD and antidepressant treatment outcomes, i.e., genetic or epigenetic variations, measures of gene expression or protein levels. Genetic variations that have been investigated in this field are mainly common single-nucleotide polymorphisms (SNPs). Common SNPs alone have been estimated to explain about 42% of the variance in antidepressant response (Tansey et al. 2013). Epigenetics refers to the study of phenotypic variations that are not caused by DNA sequence modifications and it includes gene methylation and histone modifications. Epigenetic profiles are inherited but are responsive to environmental stress, especially during early development (Jaenisch and Bird, 2003). Indeed, exposure to stressful or traumatic life events, especially early in life, is one of the strongest risk factors for the development of several psychiatric disorders, including MDD. Gene expression (mRNA levels) and protein level measures are useful complementary data to genetic and epigenetic information, since several levels of regulation occur after gene translation (i.e., post-translational modifications involving addition of functional groups or other proteins/peptides, structural changes, catabolic processes). Blood cells represent an easily available sample for gene expression studies and they share between 35 and 80% of the transcriptome with the brain (Tylee et al. 2013). A particular type of ribonucleic acid (RNA) known as microRNA (miRNA) received attention recently because miRNAs function as modulators of the degradation and translation of messenger RNA (mRNA), thus they represent a fundamental regulatory step in the process leading to protein production. Proteins can be dosed in serum or plasma and different protocols can be applied, thereby showing the results of proteomic studies are affected by preanalytical and analytical variability often resulting in poor comparability among different studies. Furthermore, new methods for quantitative proteomics were recently developed to increase the precision, robustness, and resolution of protein measurement (Li et al. 2015).

We emphasise that markers of acute depressive phases (i.e., state markers such as the expression level of inflammatory genes) are distinct from markers of susceptibility to MDD (i.e., markers of vulnerability to the disease such as genetic variants), but they partially overlap and are not always easy to distinguish. For example the expression level of some genes may be altered especially during the acute phases, but it may not completely normalise after symptom remission. The available evidence for gene expression levels was mostly obtained during the acute phase of MDD. Finally, the aetiopathogenesis of MDD is hypothesised to partially but not completely overlap with the mechanisms of antidepressant drug action, thus the sections discussing the markers of antidepressant efficacy have been separated from those discussing the markers of MDD.

2. Methods

The present review is focused on biomarkers of MDD and antidepressant responses that may be nearest to clinical applications, i.e., biomarkers that:

1. have an association with the phenotypes of interest at several "omics" levels (genetic, epigenetic and/or peripheral blood transcriptomics/proteomics);

2. are supported by at least one meta-analysis or replicated results in the same direction by at least three studies in conjunction with consistent data from translational studies.

In addition to these criteria, biomarkers that have been included in a pilot study testing clinical applicability (in terms of individual and possibly economic benefits) are also included in this review.

For an overview of markers in the first and second group see Tables 1 and 2, respectively.

Finally, a section is dedicated to new promising biomarkers, including miRNAs and, for example, methodological approaches such as polygenic risk scores (PRS). The data used for this review have been extracted from MEDLINE, EMBASE and Web of Science (ISI) and include articles published up to February 2016.

3. Serotonergic neurotransmission

Serotonin (5-HT) is known to be involved in many physiological and behavioural processes that are dysregulated in MDD, including mood, appetite, sleep, activity, suicide, sexual behaviour and cognition. The decreased levels of 5-HT metabolites in cerebrospinal fluid (CSF), coupled with the mood-lowering effects of tryptophan depletion and the efficacy of serotonin-modulating antidepressants, have supported the theory that dysfunctions of the 5-HT system are involved in the pathogenesis of MDD (Jans et al. 2007). Genetic polymorphisms are among the innate factors that modulate 5-HTergic neurotransmission, given that heritability has been reported to account for approximately 35% of the variance in CSF 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT levels (Beck et al. 1984; Oxenstierna et al. 1986).

3.1. Serotonin transporter

The serotonin transporter (SERT) is the primary target of selective serotonin reuptake inhibitors (SSRIs) and one of the main targets of other antidepressant classes. The SERT is responsible for 5-HT reuptake from the synaptic cleft and thus determines the magnitude and duration of the 5-HT synaptic signal. A reduction of SERT sites in the brain (particularly in midbrain and amygdala) of depressed patients has been demonstrated both by functional imaging (Gryglewski et al. 2014; Yeh et al. 2014) and post-mortem brain studies (Mann et al. 2000). As the binding to the SERT and the 5-HT uptake capacity remain low after recovery, low SERT activity has been suggested as a trait marker for mood disorders (Lesch 2001).

3.1.1. Genetic polymorphisms

Known polymorphisms in the gene coding for the SERT (*SLC6A4*) produce alterations in the expression level and are hypothesised to affect both the risk of affective disorders and antidepressant response. In detail, the short (S) allele (14-repeats) of the *5-HTTLPR* insertion/deletion polymorphism determines a half basal expression of SERT compared to the long (L) allele (16-repeats) (Heils et al. 1996), as well as when compared to the L allele combination with the G allele of the rs25531 polymorphism (L_G) (Hu et al. 2006). A number of genetic studies investigated the effect of the *5-HTTLPR* polymorphism on susceptibility to MDD, and two meta-analyses reported absent or negligible effects (Munafo et al. 2009; Risch et al. 2009). However, these meta-analyses included only a minority of the available studies. A more recent and comprehensive study found strong evidence that *5-HTTLPR* moderates the relationship between stress and depression, with an association between the S allele and the risk of developing depression under stress (Karg et al. 2011). Stratification of the analysis for the type of stressor showed a stronger risk effect of the S allele in cases of childhood maltreatment and medical conditions. A more recent study on a cohort of 5,249 individuals assessed at birth and followed up to the age of 18 confirmed this gene $\times$ environment interaction (Rocha et al. 2015). The interactive effect of the S allele and stress on the risk of MDD may be partly explained by the modulation of the hypothalamo-pituitary-adrenal (HPA) axis. Indeed, S allele carriers display increased basal activity of the HPA axis and S/S homozygotes show increased cortisol/corticosterone stress reactivity compared with L carriers (van der Doelen et al. 2014). Interesting findings from imaging studies include smaller hippocampal volumes in S carriers with a history of environmental adversities and higher amygdala activity in response to a number of negative stimuli in S carriers (Won and Ham, 2016). In conclusion, the *5-HTTLPR* S allele is considered to be a risk factor for MDD but only in cases of stressful environmental conditions and it is neither a required nor sufficient factor for developing MDD. Insufficient data are available in regard to the role of the triallelic locus (*5-HTTLPR* and rs25531 combination) in MDD susceptibility (Odgerel et al. 2013).

The triallelic *5-HTTLPR*/rs25531 locus was also extensively investigated as a modulator of antidepressant response. Single-photon emission computed tomography and positron emission tomography (PET) studies reported that higher pre-treatment availability and greater SSRI occupancy of the SERT might predict

Table 1. Summary of genetic, epigenetic and mRNA/protein biomarkers of major depressive disorder and antidepressant response.

Gene	Phenotype	Polymorphism(s) and allele/genotype	Epigenetic markers	Peripheral biomarker	References
SLC6A4	MDD	5-HTTLPR S allele × environmental risk factors	Elevated methylation may be a proxy marker of childhood adversities	Mixed findings	Iga et al. (2005); Pena et al. (2005); Philibert et al. (2008); Belzeaux et al. (2010); Olsson et al. (2010); Karg et al. (2011); Booij et al. (2015)
	AD response	5-HTTLPR LL in Caucasian patients treated with SSRIs	Mixed findings	Higher platelet SERT affinity constant and higher maximal uptake rate at baseline	Rausch et al. (2001); Rausch et al. (2002); Rausch et al. (2003); Fabbri et al. (2013a); Kang et al. (2013b); Myung et al. (2013); Belzeaux et al. (2014); Domschke et al. (2014); Okada et al. (2014)
HTR1A	MDD	rs6295 G allele and GG genotype; rs878567 T allele	NA	Higher expression and binding	Gonzalez et al. (2007); Kishi et al. (2013); Zhang et al. (2014)
HTR2A	MDD	rs6311 A allele; rs6313 T allele; rs7997012 GG; rs6313 in interaction with other SNPs of the region	NA	Platelet increased receptor density, but blunted receptor responsivity	Malone et al. (2007); Smith et al. (2013); Lin et al. (2014); Zhao et al. (2014)
	AD response	rs6311 G allele	NA	Possible increase of *HTR2A* mRNA and 5-HT2A receptor altered clustering	Belzeaux et al. (2010); Niitsu et al. (2013); Rivera-Baltanas et al. (2014)
BDNF	MDD	rs6265 Met allele × environmental risk factors	Higher methylation of promoter/exon I	Decreased serum and plasma BDNF levels	Fuchikami et al. (2011); D'Addario et al. (2013); Carlberg et al. (2014); Dell'Osso et al. (2014); Hosang et al. (2014); Gutierrez et al. (2015); Januar et al. (2015); Polyakova et al. (2015)
	AD response	Met/Val genotype in Asian subjects	Mixed findings	Increase in serum BDNF levels	Brunoni et al. (2008); D'Addario et al. (2013); Kang et al. (2013a); Niitsu et al. (2013); Carlberg et al. (2014); Molendijk et al. (2014); Polyakova et al. (2015)
CREB1	MDD	Possible interaction with gender and BDNF rs6265	NA	Decreased CREB DNA binding activity, CREB total protein expression and phosphorylated CREB	Zubenko et al. (2003); Utge et al. (2010); Juhasz et al. (2011); Ren et al. (2011); Lim et al. (2013)
	AD response	rs889895 GG and rs7569963 GG; possible interaction with BDNF	NA	Low baseline phosphorylated CREB, higher change of phosphorylated CREB	Koch et al. (2002); Lim et al. (2013)
GDNF	MDD	NA	NA	Decreased serum *GDNF* protein level	Lin and Tseng (2015)
	AD response	rs2973049 GG and CC preliminary evidence	NA	Increase in serum *GDNF* after antidepressant treatment	Zhang et al. (2008); Zhang et al. (2009)
CRP	MDD	rs1205 A preliminary evidence	NA	Increased serum levels	Almeida et al. (2009); Howren et al. (2009); Valkanova et al. (2013); Wium-Andersen et al. (2013); Ancelin et al. (2015)
	AD response	NA	NA	Decrease in serum level after AD treatment	Hiles et al. (2012)
IL-1β	MDD	rs16944 G allele	NA	Higher serum levels	Howren et al. (2009); Borkowska et al. (2011); Mota et al. (2013)
	AD response	rs16944 AA genotype	NA	Reduction in serum level after AD treatment; lower mRNA level at baseline	Yu et al. (2003); Tadic et al. (2008); Baune et al. (2010); Hannestad et al. (2011); Belzeaux et al. (2012); Cattaneo et al. (2013)
IL-6	MDD	rs1800795 G allele (interferon-induced depression)	NA	Higher serum levels	Bull et al. (2009); Howren et al. (2009); Liu et al. (2012); Udina et al. (2013); Valkanova et al. (2013)
	AD response	rs7801617	NA	Reduction in serum level after AD treatment	Hiles et al. (2012); Yoshimura et al. (2013)
TNF-α	MDD	rs76917	NA	Higher serum levels	Dowlati et al. (2010); Bosker et al. (2011); Liu et al. (2012)
	AD response	NA	NA	Lower baseline mRNA and protein levels	Belzeaux et al. (2012); Cattaneo et al. (2013); Powell et al. (2013)
FKBP5	MDD	rs1360780 T allele alone and x environmental risk factors	Possible hypomethylation in intron 7 region	One negative finding	Lekman et al. (2008); Lavebratt et al. (2010); Szczepankiewicz et al. (2014); Zannas and Binder (2014); Hohne et al. (2015)
	AD response	rs1360780 TT genotype	NA	Reduction in mRNA levels	Cattaneo et al. (2013); Niitsu et al. (2013); Fabbri and Serretti (2015)

SLC6A4, serotonin transporter; MDD, major depressive disorder; AD, antidepressant; HTR1A, serotonin receptor 1A; NA, no data available; HTR2A, serotonin receptor 2A; BDNF, brain-derived neurotrophic factor; CREB1, cyclic AMP response element binding protein 1; GDNF, glial cell line-derived neurotrophic factor; CRP, C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin-1β; TNF-α, tumour necrosis factor alpha; FKBP5, FK506-binding protein 52 or FKBP51.

Table 2. Biomarkers used by pilot studies investigating predictors of MDD diagnosis and antidepressant response for clinical applicability.

Phenotype	Biomarkers	Main findings	References
AD treatment outcomes (response, disability and costs)	CYP2D6, CYP2C19, CYP2C9, CYP1A2, SLC6A4 and HTR2A polymorphisms	Higher disability and costs in patients identified as "at risk" by the test; better response when the test is used to guide treatment	Hall-Flavin et al. (2013); Winner et al. (2013a, 2015)
AD efficacy	ABCB1 rs2032583 and rs2235015	Higher remission rates and lower symptom severity at the time of discharge from hospital when the test is used to guide treatment	Breitenstein et al. (2014)
AD efficacy	FKBP5 rs1360780	Worse treatment outcome in C allele carriers in the treatment as usual arm compared to the genotype-guided arm	Stamm et al. (2016)
AD treatment outcomes (response, treatment adherence, costs)	CYP2D6, CYP2C19, CYP3A4, SLC6A4, HTR2C, DRD2, CACNA1C, ANK3, COMT, MTHFR, MC4R, ADRA2A, BDNF, OPRM1 and GRIK1 polymorphisms	Not clear improvement in response or remission rates, higher medication adherence and cost savings when the test is performed	Brennan et al. (2015); Fagerness et al. (2014)
AD efficacy	CYP2D6, CYP2C19, UGT1A1, ABCB1 and ABCC1 polymorphisms	Higher remission when the test is used to guide treatment	Singh (2015)
MDD diagnosis	Serum alpha1 antitrypsin, apolipoprotein CIII, BDNF, cortisol, epidermal growth factor, myeloperoxidase, prolactin, resistin and soluble TNF-α receptor type II	Overall test accuracy of 91–94% in distinguishing patients from controls	Papakostas et al. (2013); Bilello et al. (2015)

better treatment response (Kugaya et al. 2004; Yeh et al. 2015). The most confirmed pharmacogenetic finding was an association of the S allele with worse antidepressant efficacy than the LL genotype in Caucasian patients treated with SSRIs (Porcelli et al. 2012). Relatively fewer studies genotyped the triallelic locus and they did not support a substantial role of the polymorphism on antidepressant efficacy (Fabbri et al. 2013a). Several pharmacogenetic studies (Perlis et al. 2003; Murphy et al. 2004; Popp et al. 2006; Hu et al. 2007; Smits et al. 2007; Maron et al. 2009) and one meta-analysis (Kato and Serretti 2010) reported that the S allele may also be a risk factor for the development of SSRI-induced side effects in Caucasian populations, though not for sexual dysfunction (Bishop et al. 2009; Strohmaier et al. 2011).

3.1.2. Gene methylation

DNA methylation profiles at CpG (cytosine-guanine dinucleotides) islands have been studied as a modulator of *SLC6A4* expression. Indeed, methylation at CpG islands make a gene less accessible to the molecular transcriptional apparatus that decodes the DNA sequence into mRNA and hence the production of specific proteins is reduced. An early study found a trend of association between history of MDD and increased *SLC6A4* methylation (Philibert et al. 2008), and a subsequent study reported that depressive symptoms were more common among adolescents with elevated *SLC6A4* methylation who carried the *5-HTTLPR* S allele (Olsson et al. 2010). Higher *SLC6A4* promoter methylation in subjects with a history of childhood adversities was demonstrated (Kang et al. 2013b; Booij et al. 2015) and associated with family history of depression and more severe depressive psychopathology (Kang et al. 2013b). Another recent study found no evidence of an effect of increased *SLC6A4* methylation status on the risk of MDD (Okada et al. 2014). These findings support the hypothesis that *SLC6A4* methylation status may be a proxy of childhood adversities (other than a hereditary factor) and thus it may be a useful marker of MDD susceptibility in combination with the *5-HTTLPR* S allele. *SLC6A4* methylation status was also investigated in relation to antidepressant treatment response, but with mixed results (Kang et al. 2013b; Domschke et al. 2014; Okada et al. 2014).

3.1.3. Peripheral biomarkers

The genetic and epigenetic modulation of SERT expression and function has been complemented by the study of SERT as a peripheral biomarker of MDD and antidepressant efficacy. SERT functioning can be studied in platelets, since the SERT protein expressed in platelets is considered identical to the one found in neurons, with similar structural and functional properties found in both tissues (Yubero-Lahoz et al. 2013). Higher SERT affinity constant and higher maximal uptake rate before and after antidepressant treatment were associated with treatment efficacy (Rausch et al. 2001, 2002, 2003; Myung et al. 2013). Interestingly, reductions in peripheral cell 5-HT uptake rates, cell surface SERT binding, and 5-HIAA/serotonin ratios were associated with the *5-HTTLPR* S allele, suggesting that they may represent proxy markers of the *5-HTTLPR* genotype (Singh et al. 2012). SLC6A4 expression (mRNA level) in peripheral cells (lymphocytes) was also

investigated, since lymphocytes are thought to potentially act as a neural probe for studying psychiatric disorders (Gladkevich et al. 2004). Studies on small samples of depressed patients suggested a reduction of SERT expression after antidepressant treatment (Iga et al. 2005; Tsao et al. 2006) with a possible positive correlation with response (Belzeaux et al. 2014), but opposite findings also exist (Pena et al. 2005; Belzeaux et al. 2010). The reduction of SERT expression in the rat brain was associated with antidepressant-like behaviours (Thakker et al. 2005) and key markers of antidepressant action: reduced expression and function of 5-HT1A-autoreceptors, elevated extracellular 5-HT in the forebrain and increased neurogenesis and expression of plasticity-related genes (*BDNF*, *VEGF*, *ARC*) in the hippocampus (Ferres-Coy et al. 2013). No clear association between SLC6A4 expression and MDD risk was demonstrated, since the few studies reported either negative findings (Belzeaux et al. 2010), higher expression of the gene in patients compared to controls (Iga et al. 2005) or the opposite finding (Pena et al. 2005).

3.2. Serotonin receptors

3.2.1. Serotonin receptor 1A

The 5-HT1A autoreceptor mediates the inhibition of serotonergic raphe neurons by negative feedback (Pineyro and Blier 1999), while 5-HT1A postsynaptic receptor activation has been shown to increase dopamine release in the medial prefrontal cortex (PFC), striatum and hippocampus (Sakaue et al. 2000). These findings suggest that increased 5-HT1A presynaptic and decreased postsynaptic activity may co-occur in MDD. Several studies using PET imaging demonstrated elevated 5-HT1A binding in the brain of MDD subjects, especially in the raphe (Parsey et al. 2010; Kaufman et al. 2015). 5-HT1A density distinguished male controls from depressed males with high sensitivity and specificity (both >80%) (Kaufman et al. 2015). A reduction in raphe 5-HT1A autoreceptor binding was demonstrated during SSRI treatment and was associated with symptom improvement (Gray et al. 2013).

3.2.1.1. Genetic polymorphisms The G allele of a functional promoter polymorphism in the serotonin 1A receptor gene (*HTR1A* rs6295 or C-1019G) has been associated with increased 5-HT1A expression in raphe nucleus neurons both in vitro (Lemonde et al. 2003) and in vivo using PET (Parsey et al. 2010). A recent meta-analysis found that MDD patients had higher frequencies of the GG genotype and/or G allele than controls, confirming the hypothesis derived from functional studies. The study also found that rs878567 (synonymous SNP located downstream of the gene) T allele was associated with MDD susceptibility (Kishi et al. 2013). The most recent meta-analyses that investigated the role of rs6295 in antidepressant efficacy provided negative findings (Zhao et al. 2012; Niitsu et al. 2013). Other polymorphisms in the gene were marginally investigated.

3.2.1.2. Peripheral biomarkers Higher platelet HTR1A expression was associated with MDD and severity of symptoms in drug-free patients (Zhang et al. 2014), and higher receptor binding was found in lymphocytes of depressed patients (Gonzalez et al. 2007). In contrast, a previous study did not report any difference in lymphocyte 5-HT1A receptor capacity and affinity between MDD patients and controls (Fajardo et al. 2003). No data are available in regard to antidepressant efficacy.

3.2.2. Serotonin receptor 2A

The serotonin receptor 2A (5-HT2A) is primarily a postsynaptic excitatory receptor, with wide distribution throughout the brain but with the highest density in the neocortex (Burnet et al. 1995). Both depression and suicide have been associated with greater 5-HT2A receptor binding in PFC, although data were not consistent (Stein et al. 2007). Accordingly, there is a decrease in 5-HT2A binding in cortical regions, particularly in the frontal cortex, after antidepressant treatment (Meyer et al. 2001), and compensatory downregulation of 5-HT2A receptors can prevent depressive symptoms induced by tryptophan depletion (Yatham et al. 2001).

3.2.2.1. Genetic polymorphisms Different polymorphisms (rs6311 or -1438A/G, rs6313 or 102C/T, rs7997012 and rs7333412) have been investigated within the *5-HT2A* gene with several positive but often inconsistent findings (Polesskaya and Sokolov 2002; Lin et al. 2009; Fabbri et al. 2013b; Niitsu et al. 2013; Zhao et al. 2014). Interestingly, the region downstream to the first intron of the gene was found to harbour other possibly relevant polymorphisms in the context of antidepressant response. Indeed, rs7333412, rs7324017, rs1923882 (Fabbri et al. 2014) and rs7997012 (Peters et al. 2009) are located in this region and were associated with antidepressant response in the STAR*D sample. Several other studies investigated rs7997012 with negative results (Illi et al. 2009; Kishi et al. 2009; Perlis et al. 2009; Uher et al. 2009; Horstmann et al. 2010),

although none of these included samples as large as the STAR*D study. The effect of rs7997012 and rs6313 on antidepressant efficacy was confirmed by the most recent meta-analysis (Lin et al. 2014).

3.2.2.2. Peripheral biomarkers Platelet 5-HT2A binding kinetics did not differ between MDD patients and controls (Khait et al. 2005), but seasonal variation in platelet 5-HT2A binding was demonstrated to be different in MDD patients compared to controls (Khait et al. 2002). Increased density of platelet 5-HT2A receptors may be a marker of MDD, but is more consistently associated with suicide risk (Mendelson, 2000). Despite increased receptor density, blunted receptor response was found in patients who have made high-lethality suicide attempts (Malone et al. 2007). Preliminary evidence suggested that a trend of increased HTR2A mRNA levels in peripheral lymphocytes may be observed during the first 8 weeks of antidepressant treatment (Belzeaux et al. 2010), suggesting that further studies should investigate this potential biomarker of antidepressant efficacy. Another preliminary study found that 5-HT2A receptor clustering in peripheral lymphocytes is altered in MDD and may be a biomarker of therapeutic efficacy (Rivera-Baltanas et al. 2014).

4. Neuroplasticity

Neural plasticity may be defined as the ability of neurons and neural elements to adapt in response to intrinsic and extrinsic signals. Adult neurogenesis, the development of dendritic spines, and synaptic adaptations are included among the processes defined as neural plasticity. Adult hippocampal neurogenesis has been hypothesised to play a key role in the pathogenesis and successful treatment of MDD (Wainwright and Galea 2013). Indeed, depressed patients have reduced hippocampal volume and neurogenesis that is influenced by the number of episodes and duration of the illness (McKinnon et al. 2009; Wainwright and Galea 2013). Antidepressant drugs can both prevent stress-induced decrease of hippocampal neurogenesis and reverse it (Malberg and Duman 2003; Bessa et al. 2009). Pathway analysis confirmed the enrichment of neuroplasticity pathways in MDD, with the involvement of CREB signalling in neurons, synaptic long-term potentiation and axonal guidance signalling (Jia et al. 2011; Hunter et al. 2013). Interestingly, several members of the integrin signalling pathway, including ITGB3, ZYX, ARF1, CAPNS1, CDC42, ILK, LIMS1, RAC2 and TTN were found differentially expressed between antidepressant responders and non-responders. Integrins are involved in the control of synaptic plasticity and long-term potentiation (Martins-de-Souza et al. 2014).

4.1. Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is included in the neurotrophin family of growth factors and acts as an important mediator of neuron survival, neuroplasticity and neurogenesis. BNDF is implicated in processes that modulate learning, memory and mood (Soule et al. 2006; Cowansage et al. 2010). Stress was demonstrated to decrease BDNF in mouse hippocampus, cortical and subcortical regions (Pizarro et al. 2004). Antidepressant treatment increases BDNF levels, stimulates neurogenesis and reverses the inhibitory effects of stress, thus BDNF and neurotrophins are possible targets for developing new antidepressant molecules (Masi and Brovedani 2011).

4.1.1. Genetic polymorphisms

The common SNP rs6265 (Val66Met or 196G/A) of the *BDNF* gene has received particular attention, since the Met allele decreases the processing and release of BDNF and is associated with decreased hippocampal volume in humans. However, available data do not support a significant effect of rs6265 on MDD susceptibility, as indicated by meta-analyses (Gratacos et al. 2007; Gyekis et al. 2013) that also provided negative findings for other *BDNF* SNPs (11757C/G, 270T/C, 712A/G and rs988748). Conversely, the rs6265 Met allele was demonstrated to moderate the relationship between life stress and depression (Hosang et al. 2014; Gutierrez et al. 2015).

Pharmacogenetic studies of antidepressant response mainly found a positive molecular heterosis effect of the rs6265 SNP. Indeed, the rs6265 heterozygous genotype was associated with better treatment outcome as confirmed by a recent meta-analysis (Niitsu et al. 2013), although some inconsistent or negative findings were also reported (Fabbri et al. 2013a).

4.1.2. Gene methylation

Hypermethylation of the *BDNF* gene promoter was reported in Wernicke's area (Keller et al. 2010) and peripheral blood (Kang et al. 2013a) of subjects who committed suicide. The CpG island of the *BDNF* gene upstream of exon I was found as a possible diagnostic biomarker of MDD (Fuchikami et al. 2011), and higher methylation status of the *BDNF* promoter was associated with MDD (D'Addario et al. 2013; Carlberg et al.

2014; Dell'Osso et al. 2014; Januar et al. 2015) and post-stroke depression (Kim et al. 2013).

Lower histone 3 lysine 27 (H3K27) trimethylation binding within the *BDNF* promoter (P4 region) of PFC (Chen et al. 2011) and peripheral blood (Lopez et al. 2013) was associated with antidepressant treatment, and with positive response to treatment (Lopez et al. 2013). The effect of antidepressant drugs on *BDNF* promoter methylation levels is still scarcely investigated and available data suggested a possible higher methylation status in treated versus untreated patients (Carlberg et al. 2014), but an enhanced reduction in suicidal ideation after treatment in subjects with low methylation levels (Kang et al. 2013a). Methylation levels may also be reduced in patients receiving combination treatments of antidepressants plus mood stabilisers compared to patients on antidepressant drugs alone (D'Addario et al. 2013).

4.1.3. Peripheral biomarkers

According to recent meta-analytic results, both serum and plasma BDNF levels are decreased in acute MDD, but do not differ in euthymic subjects with a history of MDD compared to healthy controls. Furthermore, antidepressant treatment of MDD patients increases serum BDNF levels in responders and remitters significantly more than in non-responders, but insufficient data are available for comparing plasma levels in responders versus non-responders (Polyakova et al. 2015). This would be an important comparison, as plasma and serum BDNF levels show at least a 100-fold difference (Rosenfeld et al. 1995). The results of prior meta-analyses reported similar results. Their analyses demonstrated lower serum BDNF concentrations in antidepressant-free depressed patients relative to both healthy controls and antidepressant-treated depressed patients (Brunoni et al. 2008; Molendijk et al. 2014) and an increase in BDNF levels after antidepressant treatment that was associated with the degree of symptom improvement (Brunoni et al. 2008).

4.2. Cyclic AMP response element binding protein 1

Cyclic AMP response element binding protein 1 (CREB1) encodes a transcription factor that induces transcription of genes in response to hormonal stimulation of the cAMP pathway. Chronic treatment with SSRIs increased the expression of phosphorylated CREB1 in the hippocampus and PFC of rats, and treatment with antidepressants also increased the levels of protein and mRNA of CREB1 and BDNF in the hippocampus of rats (Ignacio et al. 2014). As a result of such findings, CREB1 is hypothesised to upregulate the transcription of BDNF, representing an important mechanism of action of antidepressants.

4.2.1. Genetic polymorphisms

CREB1 polymorphisms have been associated with mood disorders, mainly exhibiting a significant gender effect (Zubenko et al. 2003a, 2003b; Perlis et al. 2007; Dong et al. 2009; Utge et al. 2010; Juhasz et al. 2011; Lazary et al. 2011), nevertheless not unequivocally (Burcescu et al. 2005; Hettema et al. 2009). Findings for *CREB1* and antidepressant response are also inconsistent (Murphy et al. 2004; Wilkie et al. 2007; Serretti et al. 2011; Calati et al. 2013) and negative findings have also been reported (Dong et al. 2009; Crisafulli et al. 2012; Matsumoto et al. 2014).

4.2.2. Peripheral biomarkers

CREB DNA binding activity, CREB total protein expression and phosphorylated CREB were found decreased in leukocytes of drug-free MDD patients compared with normal controls (Ren et al. 2011; Lim et al. 2013). On the other hand, no difference in mRNA levels between patients and controls was demonstrated by other studies in small samples of MDD patients (Lai et al. 2003; Belzeaux et al. 2010; Iacob et al. 2013). Another study focussed on mRNA levels in leukocytes demonstrated an opposite finding, i.e., higher CREB mRNA levels in MDD patients compared to controls (Iga et al. 2007). We underline that negative findings were restricted to gene expression studies that did not consider CREB DNA binding activity and protein levels, and were therefore unable to identify possible consequences of abnormalities during or after mRNA translation into proteins.

Animal models (Tardito et al. 2009) and in vitro data (Hisaoka et al. 2008) support the induction of CREB activation and CREB-regulatory signalling by antidepressants. Patients with low baseline phosphorylated CREB in peripheral T lymphocytes showed a greater rate of response than patients with high baseline phosphorylated CREB. A value of baseline phosphorylated CREB for predicting response was identified by Hisaoka et al. (2008) who reported a positive predictive value of 0.78, a negative predictive value of 0.64 and accuracy of 0.695. After 6 weeks of SSRI treatment, median values of change of both total and phosphorylated CREB were greater in responders than in non-responders (Lim et al. 2013). A greater increase in phosphorylated CREB in responders was confirmed by other studies using different pharmacological or

psychotherapeutic treatments (Koch et al. 2002, 2009), but no variation was reported after venlafaxine treatment (Rojas et al. 2011). Inconsistent findings were reported in regard to CREB1 mRNA variations after antidepressant treatment (increased, Belzeaux et al. 2010, or decreased, Lai et al. 2003; Iga et al. 2007, levels).

4.3. Glial cell line-derived neurotrophic factor

Glial cell line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor beta superfamily and is extensively distributed in mammalian brains, including the hypothalamus, substantia nigra and thalamus (Golden et al. 1998). GDNF promotes neurite growth (Ducray et al. 2006) and protects neurons and glial cells from oxidative or neuro-inflammatory injury (Hochstrasser et al. 2011; Jaumotte and Zigmond 2014).

4.3.1. Genetic polymorphisms

To the best of our knowledge, only one previous study investigated the possible impact of *GDNF* genetic polymorphisms on antidepressant response and no study investigated the possible effect on MDD susceptibility. In detail, rs2973049 A allele and rs2216711 T allele were associated with paroxetine non-response in a Chinese population (Wang et al. 2014), the latter showing a selective effect in females.

4.3.2. Peripheral biomarkers

Recent meta-analytic findings supported a moderate but significant decrease in serum GDNF protein level in patients with depression, with a selective effect on MDD that was not observed in other depressive disorders nor in old-age depression (Lin and Tseng 2015). A decrease in serum GDNF protein level was also found in adolescent depression (Pallavi et al. 2013), but meta-analytic data are unavailable to support this finding. GDNF mRNA in peripheral cells was reduced in individuals during a major depressive episode compared to individuals in remission and to healthy controls (Otsuki et al. 2008). Furthermore, an increase in serum GDNF concentrations was demonstrated after antidepressant pharmacological treatment (Zhang et al. 2008) and electroconvulsive therapy (Zhang et al. 2009).

5. Inflammation and HPA axis

Bi-directional mechanisms have been hypothesised to link inflammatory processes and depression. Prolonged exposure to inflammatory mediators can impair the regulation of neuroendocrine response to stress, influence the availability of monoamine neurotransmitters, and decrease neurogenesis. Conversely, both medically ill and medically healthy patients with MDD have been found to exhibit elevations in inflammatory cytokines and their soluble receptors in peripheral blood and CSF, as well as elevations in peripheral blood concentrations of acute phase proteins, chemokines, adhesion molecules and inflammatory mediators such as prostaglandins (Miller et al. 2009). A proteomic analysis in patients with MDD compared to controls confirmed that altered expression proteins involve lipid metabolism and inflammation (Xu et al. 2012). A comprehensive analytical framework based on multiple lines of evidence including association, linkage, gene expression, regulatory pathways and literature searches further support the role of inflammatory pathways in MDD (Jia et al. 2011).

5.1. C-reactive protein

C-reactive protein (CRP) is a marker of systemic inflammation and CRP phenotypes are ~40% heritable, a hereditability similar to that for major depression (Su et al. 2009). Environmental factors such as smoking, obesity and cardiovascular diseases, as well as gender differences could also be implicated and modulate the relationship between the CRP gene and depression (Hage and Szalai 2009). This may be especially important in the elderly who have a high prevalence of comorbid chronic disorders.

5.1.1. Genetic polymorphisms

Several genetic polymorphisms in the *CRP* gene have been associated with CRP levels (Almeida et al. 2009), but their association with depression remains controversial (Almeida et al. 2009; Halder et al. 2010; Luciano et al. 2010; Gaysina et al. 2011; Ancelin et al. 2015).

5.1.2. Peripheral biomarkers

High CRP serum levels were identified as a risk factor for de novo depression in women (Pasco et al. 2010), depression in men (Ford and Erlinger, 2004; Liukkonen et al. 2006; Elovainio et al. 2009; Vogelzangs et al. 2012), atypical depression (Hickman et al. 2014) and depressive symptoms (Uddin et al. 2011), especially of the somatic type (Duivis et al. 2013). Furthermore, lifetime occurrence of multiple depressive episodes was associated with higher CRP levels (Copeland et al. 2012). In a very large cohort of more than 70, 000

individuals, cross-sectional analysis demonstrated that increased CRP levels were associated with increased risk for psychological distress and depression (Wium-Andersen et al. 2013). Two meta-analyses have confirmed that major depression is associated with increased CRP levels (Howren et al. 2009; Valkanova et al. 2013).

The majority of studies demonstrated a reduction in CRP serum level after SSRI treatment (Leo et al. 2006; O'Brien et al. 2006; Pizzi et al. 2009) and treatment with non-SSRI antidepressants (Lanquillon et al. 2000; Tuglu et al. 2003). A single study reported opposite findings (Dawood et al. 2007). A meta-analysis reported a marginally significant decrease in CRP after antidepressant treatment (Hiles et al. 2012), while higher CRP levels at baseline were found to predict the persistence of depressive symptoms over 5 years (Zalli et al. 2015). Interestingly, MDD patients with high CRP levels were also reported to be less placebo-responsive and less responsive to eicosapentaenoic acid (EPA; Rapaport et al. 2015).

5.2 Interleukin-1β

Interleukin-1β (IL-1β) is a potent pro-inflammatory cytokine that acts as a key driver of both peripheral and central immune responses. IL-1β has been extensively described for its ability to act within the CNS as a modulator of hippocampal memory, as well as for its involvement in neuronal death (van de Veerdonk and Netea 2013). IL-1β was demonstrated to regulate the activity of key members of the kynurenine pathway with an effect on the availability of tryptophan and the production of toxic metabolites, explaining its modulating effect on neurogenesis in human hippocampal progenitor cells (Zunszain et al. 2012).

5.2.1. Genetic polymorphisms

The G allele of the rs16944 polymorphism (located within the promoter of the *IL-1*β gene) has been associated with SSRI non-response (Yu et al. 2003; Tadic et al. 2008; Baune et al. 2010) and with recurrent major depression (Borkowska et al. 2011). In addition, *IL-1*β promoter polymorphism rs1143627 was also associated with recurrent major depression (Borkowska et al. 2011).

5.2.2. Peripheral biomarkers

Meta-analyses reported both a positive association between IL-1β serum level and depression (Howren et al. 2009), in addition to a reduction in IL-1β serum level following antidepressant treatment (Hannestad et al. 2011). However, one meta-analysis investigated the role of IL-1β serum level in major depression and reported no evidence of association (Dowlati et al. 2010). The latter meta-analysis included fewer studies compared to the work of Howren et al. (2009) though the study did take into account potential confounders (e.g., BMI, type of depression assessment). More recent studies found that serum levels of IL-1β were higher in MDD when compared to controls or bipolar disorder subjects (Mota et al. 2013) and IL-1β mRNA was identified as a possible marker for predicting antidepressant response (Belzeaux et al. 2012). The latter finding was confirmed by an independent study that found higher baseline mRNA levels of IL-1β (+33%) in non-responders (Cattaneo et al. 2013). Platelet content of IL-1β was also associated with MDD (Hufner et al. 2014).

5.3. Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine, whose peripheral concentration was found to be inversely related to hippocampal volume in MDD (Frodl et al. 2012). The pathogenetic role of IL-6 in depression involves the acute phase of response, disorders in zinc and the erythron, HPA axis activation, induction of the tryptophan catabolite pathway, oxidative stress, autoimmune processes and neuroprogression (Maes et al. 2014).

5.3.1. Genetic polymorphisms

IL-6 polymorphisms were mainly studied in relation to specific subtypes of depression, such as post-stroke depression (Kim et al. 2012) and childhood depression (Misener et al. 2008), but with negative findings. The -174 SNP (rs1800795) is particularly interesting since individuals who carry the G allele have higher plasma concentrations of IL-6 (Zakharyan et al. 2012) and the polymorphism has been studied as a modulator of interferon-induced depression. Patients who carried the C allele (low synthesising IL-6) were reported to show fewer depressive and anxiety symptoms than those carrying the G allele, after beginning treatment with IFN-α (Bull et al. 2009; Udina et al. 2013). However, only a small study investigated the potential role of the SNP in MDD and it reported negative findings (Clerici et al. 2009), while an additional study reported no association between MDD and the SNP at -634 in a Chinese population (Hong et al. 2005). Our findings suggest further investigation of *IL-6* polymorphisms in MDD is warranted, particularly as a suggestive signal (rs7801617 SNP) for association with escitalopram response was detected in the *IL-6* gene in

the Genome-Based Therapeutic Drugs for Depression (GENDEP) genome-wide association study (Uher et al. 2010).

5.3.2. Gene methylation

An inverse correlation between methylation of *IL-6* CpGs and circulating IL-6 and CRP levels was reported in individuals with lifetime depression (Uddin et al. 2011), but findings have yet to be replicated.

5.3.3. Peripheral biomarkers

Two meta-analyses supported the association between MDD and higher IL-6 levels compared to healthy controls (Howren et al. 2009; Liu et al. 2012). Furthermore, one meta-analysis of longitudinal studies reported a modest effect of IL-6 levels on the risk of developing subsequent depressive symptoms (Valkanova et al. 2013). A pathway analysis on transcriptomic data showed that genes upregulated in MDD subjects compared to controls were enriched in IL-6 signalling pathways (Jansen et al. 2016).

Meta-analytic results also suggested a significant decrease in IL-6 serum levels after antidepressant treatment (Hiles et al. 2012), as confirmed by a subsequent study that demonstrated a correlation between plasma IL-6 levels and changes in severity of depressive state during SSRI treatment (Yoshimura et al. 2013). MDD patients with high IL-6 levels were also reported to be less placebo responsive and less responsive to EPA (Rapaport et al. 2015). IL-6 mRNA levels at baseline or after antidepressant treatment were not found to be associated with response in the GENDEP project (Cattaneo et al. 2013; Powell et al. 2013).

5.4. Tumor necrosis factor alpha

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that is hypothesised to contribute to the development of MDD and is involved in the modulation of serotonergic neurotransmission through the increase of SERT expression and activity (Malynn et al. 2013). Mice susceptible to stress-induced anhedonia show elevated expression of TNF-α and SERT in the prefrontal area (Couch et al. 2013) and SSRIs inhibit the secretion of TNF-α in human T lymphocytes (Taler et al. 2007).

5.4.1. Genetic polymorphisms

The G-308A (rs1800629) *TNF*-α polymorphism is a functional SNP whose A allele is associated with higher gene expression. Consistent with the inflammatory theory of depression, the A allele was associated with a higher risk of MDD in Korean subjects (Jun et al. 2003), but later studies either found no association with post-stroke depression (Kim et al. 2012) and single-episode depression (Haastrup et al. 2012), or reported a positive association in the opposite direction in late-life depression (Cerri et al. 2009). However, these studies were performed on small sample sizes and limited coverage of genetic variability was provided. Importantly, the Genetic Association Information Network genome-wide association study (1738 cases and 1802 controls) found the rs76917 variant showed the strongest evidence of association with MDD (Bosker et al. 2011), suggesting that studies with adequate sample size and sufficient gene coverage have increased power to demonstrate the influence of *TNF*-α on MDD. No pharmacogenetic studies are available investigating the possible association between *TNF*-α polymorphisms and antidepressant response.

5.4.2. Peripheral biomarkers

Meta-analytic results reported that TNF-α blood levels are higher in MDD compared to healthy controls (Dowlati et al. 2010; Liu et al. 2012), especially in subjects of European ancestry (Liu et al. 2012). TNF-α mRNA levels in peripheral leukocytes were also found to be higher in patients with major depression compared to controls (Tsao et al. 2006).

Higher baseline levels of TNF-α mRNA and protein were associated with non-response in the GENDEP project (Cattaneo et al. 2013; Powell et al. 2013) and findings in the inflammatory cytokine pathway at baseline and after antidepressant treatment were found to be targets of TNF (Powell et al. 2013). TNF-α mRNA levels at baseline were proposed as predictive of antidepressant response in conjunction with three other mRNAs (PPT1, IL-1β and HIST1H1E) (Belzeaux et al. 2012). A meta-analysis antecedent to these studies found no clear evidence of reduction in TNF-α serum levels after antidepressant treatment, but found some evidence that SSRIs may reduce TNF-α serum levels (Hannestad et al. 2011).

5.5. FK506-binding protein 52 or 51

The *FKBP5* (FK506-binding protein 52 or FKBP51) gene encodes for a member of the family of large immunophilins. The encoded protein was reported to act as a scaffolding protein regulating Akt activity that might have implications in the development and treatment of depression (Duman and Voleti 2012). The FKBP51 protein is a co-chaperone for glucocorticoid receptor

(GR) maturation, modulating its sensitivity and thus playing a role in the regulation of stress response. Further supporting this notion are studies showing that increased expression of the *FKBP5* gene confers elevated GR resistance (Binder, 2009) and that glucocorticoids induce *FKBP5* expression (Vermeer et al. 2003). Rats exposed to chronic mild stress show increased expression of *FKBP5* as well as enhanced cytoplasmic levels of GR, primarily in ventral hippocampus and PFC. Chronic treatment with the antidepressant duloxetine is able to normalise such alterations (Guidotti et al. 2013).

5.5.1. Genetic polymorphisms

A number of studies reported an *FKBP5* × environment interaction in predicting the risk of depression, which is consistent with the observation that *FKBP5* is responsive to stressor exposure and increases glucocorticoid levels by modulating GR sensitivity (Zannas and Binder 2014). More precisely, rs9296158, rs4713916, rs1360780, rs9470080 and rs3800373 have been found to be involved in gene × childhood trauma interactions, likely through mediating epigenetic modifications (see Section 4.5.2). The rs1360780 T allele was identified as the risk allele by three studies, the rs9470080 T allele by two studies, and the rs3800373 C allele by one study (Zannas and Binder 2014). Some studies did not take into account *FKBP5* × environment interactions and three studies found that the rs1360780 T allele was associated with increased risk of depression (Lekman et al. 2008; Lavebratt et al. 2010; Szczepankiewicz et al. 2014), two studies found an effect of rs4713916 (Zobel et al. 2010; Szczepankiewicz et al. 2014), and non-replicated findings were reported for rs9470080, rs9296158 (Szczepankiewicz et al. 2014) and rs3800373 (Zobel et al. 2010).

Despite controversial pharmacogenetic findings being reported for the *FKBP5* gene, results obtained in a large sample of Caucasian subjects suggested that rs1360780, rs3800373, rs4713916 and rs352428 polymorphisms may modulate antidepressant response (Fabbri and Serretti, 2015). The effect of rs3800373 and rs1360780 on antidepressant response was confirmed in subjects of Caucasian ethnicity by a recent meta-analysis (Niitsu et al. 2013). Interestingly, rs1360780 TT genotype showed FKBP5 protein levels that were twice as high as C allele carriers in vitro (Binder et al. 2004). This genotype was associated with faster response, modulation of *FKBP5* expression, lower ACTH response in the combined dexamethasone-suppression/CRH-stimulation test and, hypothetically, a faster restoration of normal HPA axis function (Binder et al. 2004). Furthermore, rs352428 was demonstrated to be a functional polymorphism that may alter transcription factor binding (Ellsworth et al. 2013) and thus gene expression.

5.5.2. Gene methylation

DNA methylation in the rs1360780 region in intron 7 of *FKBP5* showed a non-significant trend toward genotype-dependent CpG methylation differences (hypomethylation) among subjects with a lifetime history of MDD (Hohne et al. 2015). Consistently, exposure to child abuse leads to a significant demethylation of CpGs in the functional glucocorticoid response elements (GREs) in intron 7 of the *FKBP5* gene. Demethylation of these CpGs leads to an enhanced induction of *FKBP5* transcription by GR agonists and is associated with GR resistance (Klengel et al. 2013). The exposure to stressful events during childhood is hypothesised to induce local CpG demethylation mediated by GR binding to GREs, followed by a depressed transcriptional response to subsequent glucocorticoid exposure. Thus, stressor exposure results in higher cortisol release and GR activation in rs1360780 risk allele carriers (Zannas and Binder, 2014).

Of interest, the spindle and kinetochore complex subunit 2 (SKA2) protein is similar to FKBP51, in that it interacts with the GR. The C allele of the *SKA2* genetic polymorphism rs7208505 (C/T) can be epigenetically modified via addition of a methyl group. The combination of genetic variation and epigenetic modification at rs7208505 has been associated with MDD and suicide and this finding has been replicated in both postmortem brain tissue and peripheral blood samples (Guintivano et al. 2014).

5.5.3. Peripheral biomarkers

In healthy subjects the rs1360780 CC genotype showed an increase of FKBP5 mRNA levels after stress exposure compared to CT or TT genotypes, despite no genotype effect on mRNA expression found in remitted MDD patients (Hohne et al. 2015). A reduction in FKBP5 mRNA levels after 8 weeks of antidepressant treatment was associated with successful antidepressant response (Cattaneo et al. 2013).

6. Clinical applications: pilot studies

Evaluation of the reliability versus cost/effectiveness ratio of using biomarkers in clinical settings is a critical phase for the translation of research into tailored treatments. Studies are investigating the clinical

usefulness of genetic testing for the prediction of antidepressant treatment outcome, in addition to serum-based tests analysing the expression levels of nine genes proposed for use in MDD diagnosis. Genetic tests for use in predicting antidepressant response include genes involved in antidepressant metabolism (the cytochrome P450 (*CYP*) superfamily; Porcelli et al. 2011), antidepressant transport (ABCB1) and antidepressant drug targets. For example, the GeneSight assay was designed to predict antidepressant response and side effects on the basis of polymorphisms in *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *SLC6A4* and *HTR2A*. Patients classified as "at risk" according to this genetic test were reported to have 69% more total health care visits, 67% more general medical visits, greater than 3-fold more medical absence days, and greater than 4-fold more disability claims (Winner et al. 2013a). Furthermore, the GeneSight test was reported to double the likelihood of response compared to treatment as usual in a small prospective randomised double-blind trial (Winner et al. 2013b) and similar findings were obtained in a larger open-label study (Hall-Flavin et al. 2013). Finally, the GeneSight test was recently demonstrated to save $1,035.60 more in total medication costs (both CNS and non-CNS medications) over 1 year compared to a non-tested standard care cohort (Winner et al. 2015). In comparison, the commercial pharmacogenetic Genecept Assay includes polymorphisms in *CYP2D6*, *CYP2C19*, *CYP3A4*, *SLC6A4*, *HTR2C*, *DRD2*, *CACNA1C*, *ANK3*, *COMT*, *MTHFR*, *MC4R*, *ADRA2A*, *BDNF*, *OPRM1* and *GRIK1*. This assay was tested in a naturalistic study (Brennan et al. 2015) that did not include a comparison arm receiving treatment as usual, thus statements regarding the clinical benefits of the test are particularly difficult. A study that did include patients treated as usual reported higher medication adherence and cost savings in patients who underwent the test (Fagerness et al. 2014). Lastly, the CNSDose pharmacogenetic test includes polymorphisms in *CYP2D6*, *CYP2C19*, *UGT1A1*, *ABCB1* and *ABCC1* genes and in a randomised trail patients receiving genotype-guided treatment showed a 2.52 greater probability of remission (Singh 2015). Of note, replication by the same investigators was found for the GeneSight test, but no independent validation of any of the above reported results was found.

Two studies without commercial interest investigated the clinical benefits of a genotype-guided treatment versus treatment as usual. The first study investigated the clinical usefulness of polymorphisms in *ABCB1*, the gene encoding for the P-glycoprotein (or P-gp). P-gp is an ATP-dependent drug efflux pump for xenobiotic compounds which limits uptake and accumulation of some lipophilic drugs (including several antidepressants) into the brain. In the genotype-guided treatment arm *ABCB1* gene test results (rs2032583 and rs2235015 SNPs) were implemented into the clinical decision making process and this group showed higher remission rates and lower symptom severity at the time of discharge from hospital as compared to patients without *ABCB1* testing (Breitenstein et al. 2014). Furthermore, antidepressant dose adjustments based on rs2032583 and rs2235015 were shown to affect antidepressant plasma concentration and symptom improvement in a consistent way (Breitenstein et al. 2016). A more recent study investigated the clinical usefulness of *FKBP5* rs1360780 genotyping and it found that the risk allele showed a worse outcome in the treatment as usual arm compared to the genotyped-guided treatment arm (Stamm et al. 2016). Unfortunately, these studies investigating *ABCB1* polymorphisms and *FKBP5* rs1360780 clinical usefulness lack independent replication and did not provide any cost/benefit ratio estimation.

As reported above, a biomarker panel has been developed using serum-based testing to predict MDD. Results are interesting, but replication by independent groups is also lacking. The test includes nine biomarkers (alpha1 antitrypsin, apolipoprotein CIII, BDNF, cortisol, epidermal growth factor, myeloperoxidase, prolactin, resistin and soluble TNF-α receptor type II) and it demonstrated a sensitivity and specificity of 91.7 and 81% in differentiating between MDD and healthy controls, respectively (Papakostas et al. 2013). Similar findings were obtained in a further study by the same authors, with an overall test accuracy of 91–94% depending on the sample (Bilello et al. 2015). No replication by independent investigators is available.

7. Innovative biomarkers and methodological strategies

New research perspectives recently emerged in terms of both biomarker type and methodological approach. In particular, miRNAs were found to act as pivotal regulators of mRNA degradation and thus mRNA translation, providing complementary information to other biomarkers. miRNAs may also represent a relatively accessible method to therapeutically manipulate gene expression, making them particularly interesting targets for future treatments. Indeed miRNAs can be detected in body fluids such as blood and they show unexpected stability (Dwivedi 2016). For example, miR-16

was found to modulate SERT expression in different areas of the brain in response to antidepressants (Baudry et al. 2010). In mice fluoxetine was demonstrated to decrease the levels of miR-16 in the noradrenergic locus coeruleus and in the hippocampus, resulting in higher SERT expression in these areas, increased BDNF secretion and hippocampal neurogenesis (Launay et al. 2011). In comparison, miR-135 has been reported to modulate SERT as well as HTR1A expression and its levels are increased in mice after the administration of antidepressants (Issler et al. 2014). Genetically modified mouse models, expressing higher or lower levels of miR-135, demonstrated major alterations in anxiety- and depression-like behaviours, 5-HT levels, and behavioural response to antidepressant treatment. Finally, miR-135a levels in blood and brain of depressed human patients were demonstrated to be lower compared to controls (Issler et al. 2014). A recent study including data on humans reported miR-1202 as a promising marker of MDD and antidepressant response (Lopez et al. 2014). Interestingly, the targets of miR-1202 are genes involved in neurological processes associated with the pathogenesis of MDD, including the *GRM4* gene that has been implicated in the regulation of anxiety-related behaviours (Pilc et al. 2008; Davis et al. 2012). Finally, a recent review reported a comprehensive overview in regard to miRNA in MDD and antidepressant treatment (Dwivedi 2016).

Under the methodological point of view, PRS are worth note because they represent the most recent attempt to capture the complexity of disease traits, such as those found in MDD. PRS are obtained through the sum of the effect sizes of SNPs with a certain level of association with a particular trait. Thus, they attempt to classify patients within a risk spectrum, or in other words to assign to each patient a risk of developing the trait in question (i.e. response to a drug or disease status).

Previous studies using this approach found that a genome-wide polygenic score was able to explain only small percentages of the variance in depression; for example, 1% was reported in elderly cohorts (Demirkan et al. 2011; Musliner et al. 2015) and 0.2% when considering a long-term average depression score (Chang et al. 2014). Phenotypic and environmental heterogeneity may explain these low percentages, but the available evidence excluded that stressful life events may interact with PRS associated with depression (Musliner et al. 2015). However, PRS were reported to have higher effect sizes as depressive symptom severity increased (Chang et al. 2014). Other possible sources of heterogeneity were not investigated.

Genome-wide complex trait analysis is an alternative method that estimates the proportion of phenotypic variance on the basis of the genetic relatedness between individuals. Using this method, common variants were estimated to explain 42% of individual differences in antidepressant response and 43% when considering only SSRIs (Tansey et al. 2013). In contrast, a polygenic score based on a meta-analysis of the GENDEP and MARS projects predicted only between 0.5 and 1.2% of variance in improvement and remission in the STAR*D sample (GENDEP, MARS, STAR*D Investigators, 2013), suggesting a significant but not exciting overlap in terms of genetic variants involved across different MDD samples.

8. Conclusion

Several biomarkers of MDD and antidepressant response have been replicated at genetic, epigenetic and/or transcriptomic/proteomic levels (Table 1), despite controversial findings often being reported. Genes consistently found in the replicated studies (e.g., *SLC6A4* and *HTR2A*) have been included in the first genetic tests investigated for clinical applicability (Table 2). It is important to underline that a favourable cost/benefit ratio has not been clearly demonstrated for any of the commercially available pharmacogenetic tests and currently no established clinical indications exist. The GeneSight test provided encouraging results, but the details regarding the algorithm used to classify patients according to their genotype were not published. Therefore, replication of the results by independent investigators has not been possible. The multi-assay, serum-based test that included nine biomarkers for MDD diagnosis (Papakostas et al. 2013) was performed on patients who already met the clinical DSM criteria for MDD, thus the cost/benefit balance of this test is not clear. Furthermore, the predictive properties of the serum-based test have not been replicated by an independent group of investigators. MDD may be too heterogeneous to be useful for the study of biomarkers. Given the broad nature of MDD, which most likely includes patients with many diverse aetiologies, it would be of interest to identify biomarker panels to assist in identifying depression subtypes, such as melancholia or psychotic depression. Dimensional approaches to understand the risk and expression of mood disorders provide a different perspective for the development of future diagnostic/response-predictive tests. The Research Domain Criteria (Insel et al. 2010) focus on constructs under the negative valence systems domain (i.e., acute threat, potential threat, sustained threat, loss and frustrative non-

reward) and provide dimensional criteria that are aimed at facilitating the identification of biomarkers of biologically homogeneous alterations that exist across disorders. As we specified in the Introduction, it is not always easy to distinguish between markers of acute depressive phases (markers of state) and markers of susceptibility to MDD, particularly for transcriptomic markers, and future studies investigating this issue are warranted. Finally, the integration of different types of biomarkers and the use of more complex multi-marker panels (that could be obtained through PRS, for example) represent interesting strategies to pursue for future clinical applications.

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