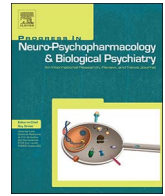




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Targeting aggression in severe mental illness: The predictive role of genetic, epigenetic, and metabolomic markers

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ABSTRACT

Human aggression is a complex and widespread social behavior that is overrepresented in individuals affected by severe mental illness (SMI), such as schizophrenia (SCZ), bipolar disorder (BD), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). A substantial proportion of the liability threshold for aggressive behavior is determined by genetic factors, and environmental moderators might precipitate the manifestation of this behavioral phenotype through modification of gene expression via the epigenetic machinery. These specific alterations in the genetic and epigenetic make-up of aggressive individuals might determine distinct biochemical signatures detectable through metabolomics. An additional pathophysiological component playing a role in aggressive behavior might be determined by alterations of gut microbiota. Here, we present a selective review of human data on genetic, epigenetic, and metabolomic markers of aggressive behavior in SMI, discussing also the available evidence on the role of microbiome alterations. Clinical implication of these evidences, as well as future perspectives, will be discussed.

1. Introduction

Human aggression and violence are complex and widespread social behaviors (Siever, 2008). According to the World Health Organization (WHO) violence/aggression is among the leading causes of death worldwide for people aged 15–44 (World Health Organization, 2002), determining a substantial economic burden on the healthcare system (World Health Organization, 2002). In presenting key measures (incidence, prevalence, predicting power of trait-associated clinical, genetic/epigenetic, and metabolomic variables) of behavioral phenotypes such as violence or aggression, definitions matter. Although some authors suggest that violence might be a specific form of aggression (Valzelli, 1982), the vast majority of researchers in the field consider the two terms interchangeable, at least with regard to human behavior (Volavka, 2002). Since we elected to review data collected in human samples, we will henceforth use aggression (or aggressive behavior) to indicate both terms.

One key aspect of human aggression is that tends to be overrepresented in individuals affected by severe mental illness (SMI), particularly schizophrenia (SCZ), bipolar disorder (BD), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), compared to unaffected populations (Pulay et al., 2008).

Several sets of epidemiological findings support the latter association. Patients affected by SMI commit 1 in 20 violent crimes (Fazel and Grann, 2006). This figure is consistent with the higher risk of homicidal violence found in SMI patients compared to unaffected subjects (Eronen et al., 1996). Furthermore, individuals hospitalized in psychiatric wards have a higher risk of committing a criminal offense compared to subjects with no history of psychiatric admission (Hodgins et al., 1996). And rates of aggression in SMI patients might range from 26% to 84% (Tsiouris et al., 2011).

Undoubtedly, the prevalence of aggressive behavior varies depending on the specific SMI considered. Epidemiological estimates show that the rates of aggressive behaviors might range from 5.7% in ADHD (Gonzalez et al., 2013), 13.9% in male SCZ patients (Fazel et al., 2014), 25% in BD type 1 (Pulay et al., 2008), to reach 68% in ASD (Kanne and Mazurek, 2011). Although impacted by the lack of uniformity in the methodology used for the identification of aggressive behavior (i.e. retrospective self-reported information versus prospective data collection based on structured assessment tools), these figures show unequivocally a substantial raise compared to the rates observed in unaffected populations. Several mediating mechanisms, such as comorbid substance abuse, presence of childhood trauma, poor coping/stress, and behavioral instability, might partly explain the relationship between

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aggression and SMI (Edlinger et al., 2014; Bruce and Laporte, 2015; Coid et al., 2015). Indeed, Edlinger et al. (2014) found that SCZ patients with comorbid psychoactive substance use admitted to acute inpatient units had the highest risk of aggressive behavior compared to patients with affective disorders. Bruce and Laporte (2015) found that SMI patients with history of child trauma had significantly higher odds of engaging in aggressive behaviors compared to those without such history. Finally, Coid et al. (2015) found that violent ideation, behavioral instability, and poor/coping stress were all explanatory variables of the association between aggression and SMI.

1.1. Developmental trajectories of aggression in SMI

The manifestation of aggression in SMI appears to have developmental trajectories specific to each disorder. For instance, SCZ individuals might manifest aggressive behaviors in the context of acute psychopathological dysregulation such as command hallucinations to harm others or paranoid delusions (state-related precipitating factors) (Volavka, 2013; Darrell-Berry et al., 2016). Alternatively, conditions related to personality traits anteceding the onset of psychiatric disorders (particularly BD and ADHD, but also SCZ), such as antisocial conduct disorder, might significantly increase the risk of developing aggressive behavior (Volavka, 2013; Swanson et al., 2008; Gudjonsson et al., 2014; Swann et al., 2011). Both state- and trait- related factors might modulate the liability threshold for the development of aggressive behavior set by the genetic and epigenetic risk components. Indeed, environmental factors can determine modification of the encoded genetic information, by altering gene expression regulatory machinery through epigenetic factors (Fig. 1). State- and trait- related factors are also modulated by these mechanisms, suggesting a constant

longitudinal modulation of the liability threshold for the development of aggressive behavior.

1.2. Genetic and epigenetic of aggressive behavior

A substantial proportion of the liability threshold for aggressive behavior is determined by genetic factors in the general population. Large longitudinal twin studies have shown a heritability of 50% to 80% for this behavioral trait (Porsch et al., 2016). Consistently, molecular genetic data using genome-wide complex trait analyses (GCTA) found that common genetic variation explains 10% to 54% of phenotypic variation in aggressive behavior in children, with the most significant genome-wide association signal on chromosome 2p12 (Pappa et al., 2016). Twin studies have also shown that shared environment might explain up to 20% of the phenotypic variation in aggression (Porsch et al., 2016). As introduced previously, environmental moderators might modulate the liability to aggressive behavior determined by genetic factors during the longitudinal developmental trajectory starting from toddlerhood to adolescence (Nantel-Vivier et al., 2014; Hay et al., 2014; Tremblay et al., 2004; Cote et al., 2006). It is plausible that these environmental moderators, by acting on this considerable genetic liability, might facilitate the manifestation of the behavioral phenotype. Importantly, the exposure to these moderators might happen before birth (Tremblay and Szyf, 2010). In fact, it has been established that having a mother with early onset antisocial behavior is a potent predictor of high levels of physical aggression in children assessed longitudinally from birth to 42 months of age (Tremblay et al., 2004). Similarly, factors such as low income, presence of mothers who smoked during pregnancy, mothers' coercive parenting behavior, and family dysfunction predict the manifestation of aggressive behavior in children (Tremblay et al., 2004). As shown in Fig. 1, this moderation might be exerted through the epigenetic machinery. Of note, specific epigenetic signatures of peripheral white blood cells seem to correlate with the manifestation of physical aggression during childhood (Wang et al., 2012). And recent epigenome-wide analysis in peripheral white blood cells of a large twin sample showed a positive relationship between DNA methylation levels and aggressive behavior near the trichorhinophalangeal syndrome I (*TRPS1*) gene on chromosome 8 and between the non-coding RNA *PARD6G* antisense RNA 1 (*PARD6G-AS1*) and the activity-dependent neuroprotective protein 2 gene (*ADNP2*) on chromosome 18 (van Dongen et al., 2015).

These specific alterations in the genetic and epigenetic make-up of aggressive individuals might determine distinct alterations in the physiological pathways of the Peripheral and Central Nervous System (PNS and CNS) regulating behavioral control.

1.3. Detection of biochemical signals of aggressive behavior

One crucial issue in the study of complex traits such as psychiatric disorders or behavioral phenotypes is the detection of biological signals that might predate the manifestation of symptoms, and consequently help enabling preventive strategies. Biochemical signatures of illness-associated alterations in CNS and PNS might be detected through the analysis of peripheral set of metabolites (metabolome) (Hagenbeek et al., 2016). A recent data synthesis has shown that biochemical markers, such as inflammation markers, neurotransmitters, lipoproteins, and hormones of various classes, are significantly altered in individuals with aggressive behavior (Hagenbeek et al., 2016). It is conceivable that the joint analysis of genetic, epigenetic, and metabolomic data might help refining the prediction of aggressive behavior particularly in at risk populations such as those affected by SMI.

One final introductory remark concerns the hypothesis that an additional pathophysiological component playing a role in aggressive behavior might be determined by distinct alteration of gut microbiota. It is well established that intestinal microbiota and the brain are

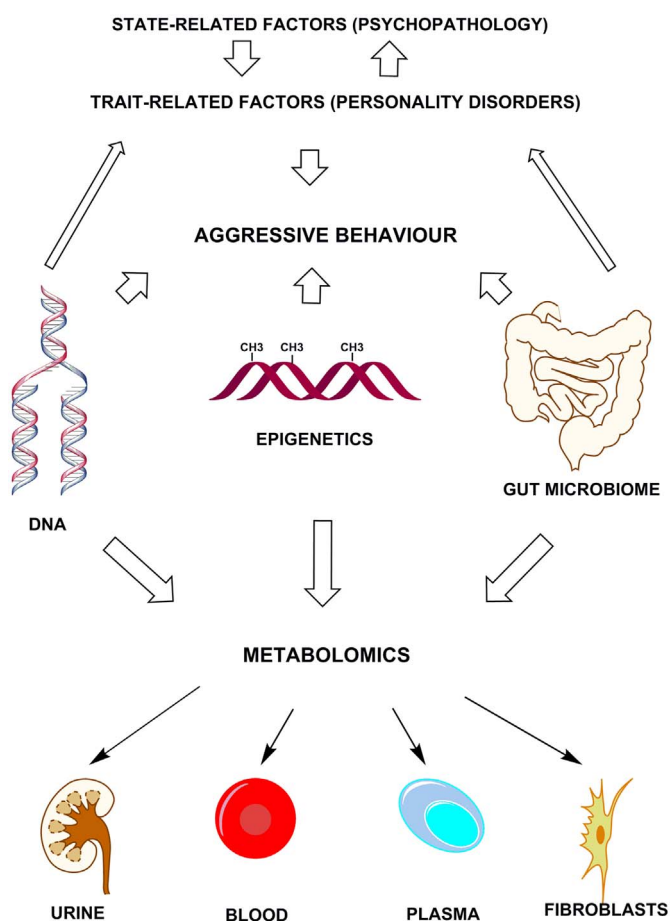


Fig. 1. Representation of the interplay of genetic, epigenetic, and microbiomic factors in aggressive behavior, and role of metabolomics in identifying trait-related biomarkers.

Table 1
Candidate gene association studies of aggressive behavior in severe mental illness.

Severe mental illness	Candidate gene	Polymorphism	Type of genotype-phenotype association	Reference
Schizophrenia	<i>HTR2A</i>	rs6311 (– 1438 A/G)	A/G carriers had better emotional regulation	(Lo et al., 2010)
	<i>TPH1</i>	rs1800532 (A218C)	No association with aggressive behavior	(Kim et al., 2010)
	<i>BDNF</i>	rs6265 (Val66Met)	BDNF Met/Val genotype were more aggressive than patients with Val/Val genotype	(Spalletta et al., 2010)
	<i>BDNF</i>	rs6265 (Val66Met)	No association with aggressive behavior	(Chung et al., 2010)
	<i>BDNF</i>	rs6265 (Val66Met)	No association with aggressive behavior	(Guan et al., 2014)
	<i>MTHFR</i>	rs1801131, rs1801133	T-allele polymorphism of rs1801133 and the T-C haplotype were associated with aggressive behavior	(Dong et al., 2012)
Autism spectrum disorder	<i>NRGN</i>	rs12807809	CC genotype associated with higher aggression compared to other genotypes	(Su et al., 2015)
	<i>ITGB3</i>	rs5918	TT genotype associated with symptoms of aggression	(Schuch et al., 2014)

HTR2A: 5-Hydroxytryptamine (Serotonin) Receptor 2A; TPH1: tryptophan hydroxylase 1; BDNF: brain-derived neurotrophic factor; MTHFR: methylenetetrahydrofolate reductase; NRGN: neurogranin; ITGB3: β 3 integrin.

connected bidirectionally, and that alterations in the gut microbiota might lead to behavioral disruption, as well as influencing the susceptibility to SMI with externalizing behaviors such as ASD (Collins et al., 2012; Cryan, 2016; Sherwin et al., 2016). This is consistent with recent experimental data in *Drosophila melanogaster* showing that modifications of microbiome might reduce aggressive behavior in male flies (Rohrscheib et al., 2015). Interestingly, in mice gut microbiota appeared to be crucial for the programming and presentation of distinct normal social behaviors, including social motivation and preference for social novelty, which are generally altered in neurodevelopmental disorders such as SCZ and ASD (Desbonnet et al., 2014).

These data suggest that alterations in the microbiome might contribute to the development of aggressive behavior, particularly in individuals affected by SMI.

1.4. Aims and methodology of literature search

In our study, we aim to selectively review the recent evidence about genetic, epigenetic, and metabolomic predictors of hetero-aggression in SMI, namely SCZ, BD, ASD, and ADHD, focusing on human data. Each section of this review will present, whenever available, data concerning a specific SMI, covering genetic, epigenetic, and metabolomic evidence. Specifically, we first review the main findings on genetics of aggressive behavior in SMI, focusing, whenever available, on genome-wide association studies (GWAS) and genome-wide linkage studies. If genome-wide data were not available, such as in SCZ and ASD, we performed a systematic electronic search in Medline for candidate gene studies published in the last 6 years using the following terms “schizophrenia” OR “autism spectrum disorder” AND “genetics” AND “aggression” OR “violence”. We then present a brief overview of epigenetic of aggression in SMI, focusing on conduct and antisocial disorders. Next, we used the same search strategy employed for genetic studies to review human metabolomic data. However, given the lack of studies exploring metabolomics of aggression in SMI, we used a psychiatric disorder commonly associated with aggressive behavior, namely ASD, as a phenotypic proxy (search terms: OR “autism spectrum disorder” AND “metabolomics” AND “aggression” OR “violence”; temporal frame: last 6 years). In addition, we review the available evidence on the role of microbiome alterations in modulating aggressive behavior in SMI, presenting human and animal data. Finally, we will assess the clinical implications of this evidence, discussing the feasibility of integrating these data in predictive models for aggressive behavior, leading to effective preventive strategy and tailored treatment in aggressive SMI patients. The literature search was performed on May 2016.

2. Genetics of aggression in psychiatric disorders

The presence of high heritability estimates of aggressive behavior prompted researchers to identify genetic determinants of risk through

the use of candidate gene association studies and, more recently, with hypothesis-free genome-wide analysis. The latter approach appears to be more suitable for the study of the genetic architecture of aggressive behavior than the former, since recent meta-analytical estimates of 277 independent association signals on 31 candidate genes did not demonstrate the presence of any significant predictor of risk for aggression (Vassos et al., 2014). Far from being unexpected, this outcome is consistent with what has been typically observed in other complex traits such as psychiatric disorders. Of interest, Zhang-James and Faraone (2016) have recently performed a systematic search of the Online Mendelian Inheritance in Man (OMIM) database to identify all genes with rare variants causative of aggressive behavior in human Mendelian disorders and compared them with a panel of known candidate genes for aggression developed by experts of the European Union (EU) funded Aggessotype Consortium. The comparative analysis of these two gene lists, and of the associated biological pathways, showed an overlap in monoamine oxidase A (*MAOA*) gene, as well as in the glutamate ionotropic receptor AMPA type subunit 3 (*GRIA3*) gene, corresponding to shared dysregulation of the following pathways: serotonin, dopamine and gamma-aminobutyric acid (GABA) signaling, long-term depression and c-AMP response element binding protein (CREB) signaling in neuron (Zhang-James and Faraone, 2016). In summary, these results highlight the presence of specific genetic signatures of aggressive behavior, which might result in substantial neurobiological alteration predisposing to behavioral dysregulation, particularly in individuals with SMI. Both candidate gene and genome-wide association studies results are summarized in Tables 1 and 2, respectively.

2.1. Schizophrenia

Since to date there are no GWAS on aggressive behavior in SCZ, the available data on genetic determinants of aggressive behavior in SCZ are mostly based on hypothesis-driven candidate gene association studies (Soyka, 2011). Following the hypothesis that the neurobiological underpinnings of aggression might lie in alterations of dopaminergic and serotonergic signaling pathways (Soyka, 2011), a number of studies examined the contribution of polymorphisms within genes encoding for elements of these pathways to the risk of developing aggressive behaviors in SCZ patients (Table 1). In a study exploring the role of the serotonin 2A receptor (*HTR2A*) rs6311 polymorphism in modulating emotional management in SCZ, Lo et al. (2010) found that heterozygotes (A/G genotype) individuals performed better than G/G (but not A/A) homozygotes carriers in managing emotions. This result suggests a role of variation in *HTR2A* gene in emotional regulation, a component that, if dysregulated, might predispose to aggressive behavior.

Another study investigated the association between the A218C tryptophan hydroxylase 1 (*TPH1*) gene and aggression in 61 aggressive, 104 non-aggressive Korean SCZ patients, and 335 healthy controls (Kim

Table 2

Top association signals in genome-wide linkage and case-control association studies of aggressive behavior in severe mental illness.

Severe mental illness	Study design	Results	Reference
Bipolar disorder	Linkage analysis GWAS	Suggestive linkage on chromosomal regions 1p21.1, 6p21.3, and 8q21.13 rs17190927 in the <i>SPTLC3</i> gene	(Doyle et al., 2010) (Alliey-Rodriguez et al., 2011)
	Gene expression	Three TNF gene expressions were inversely correlated with aggression, while one TNF gene (<i>TNFAIP3</i>) expression was positively correlated with aggression	(Barzman et al., 2014)
Autism spectrum disorder	CNV and SNV analysis	Five truncating variants of <i>ZMYND11</i> gene in individuals with aggression and ASD	(Coe et al., 2014)
Attention-deficit/Hyperactivity disorder	Polygenic risk score analysis	ADHD polygenic risk score increased with number of aggressive conduct disorder symptoms	(Hamshere et al., 2013)
	GWAS	rs7204436 in an intergenic region on chromosome 16, rs1278352 of <i>ADAM12</i> gene on chromosome 10, and rs12370275 in an intergenic region on chromosome 12 nominally associated with aggressive behavior	(Aebi et al., 2016)
	GWAS	rs10826548, within a long noncoding RNA gene, and rs35974940 in <i>NTM</i> gene associated with aggressiveness in adult ADHD	(Brevik et al., 2016)

GWAS: genome-wide association study; CNV: copy number variation; SNV: single-nucleotide variant; *SPTLC3*: serine palmitoyltransferase, long-chain base subunit 3; RNA: ribonucleic acid; TNF α : tumor necrosis factor-alpha; *ZMYND11*: zinc-finger MYND domain 11; ADHD: Attention-deficit/Hyperactivity disorder; *ADAM12*: a disintegrin and metalloprotease 12; *NTM*: neurotrimin.

et al., 2010). The authors did not find any association of the studied polymorphism with regard to aggressive behavior in this cohort of SCZ patients, although, interestingly, this same polymorphism appears to predict higher propensity to verbal aggression in major depressive disorder (MDD) patients (Koh et al., 2012).

Concerning the dopaminergic system, researchers focused on the catechol-*O*-methyltransferase (*COMT*) gene, encoding for the enzyme responsible for the catabolism of catecholamines (Gu et al., 2009; Tosato et al., 2011; Mohamed et al., 2015). Gu et al. were not able to identify an association between individual polymorphism within *COMT* gene and aggression in 252 Chinese Han SCZ patients (Gu et al., 2009). However, they found an overrepresentation of the haplotype A-A-G (SNPs rs4680, rs737865, and rs165599) in aggressive compared to non-aggressive SCZ patients (Gu et al., 2009). Tosato et al. (2011) showed that SCZ patients carrying Met/Met genotypes had the highest score at the overt aggression scale compared to Val/Val and Val/Met carriers, suggesting that *COMT* might influence aggressiveness in SCZ. Of interest, the latter result has been confirmed by two subsequent independent meta-analyses (Singh et al., 2012; Bhakta et al., 2012). A more recent study did not find, however, an association between rs4680 Val158Met and aggression in Malaysian SCZ patients (Mohamed et al., 2015). Although there is discrepancy across studies, the association of Met/Met rs4680 carriers with aggression in SCZ appears to be supported by quantitative data synthesis. In addition, a recent meta-analysis showed that the integration of data on blood-oxygen-level dependent functional magnetic resonance imaging (BOLD-fMRI) and on rs4680 genotypic status increased substantially the predictive power for aggression in SCZ (Tang et al., 2017). A summary of these data, along with findings on *COMT* and aggression in other psychiatric disorders,

can be found in Table 3.

Another set of studies investigated the role of the gene encoding for brain-derived neurotrophic factor (BDNF), a key regulating protein of neuroplasticity and neuronal growth in CNS, in aggressive behavior in SCZ (Spalletta et al., 2010; Chung et al., 2010; Guan et al., 2014). In fact, Spalletta et al. (2010) studied the Val66Met *BDNF* gene polymorphism showing that SCZ patients carrying Met/Val genotype were more aggressive than patients with Val/Val genotype, as shown by higher scores at the modified overt aggression scale (MOAS) (Kay et al., 1988). This finding is discordant, however, with the work of Chung et al. (2010) and Guan et al. (2014), which did not find an association between the Val66Met *BDNF* gene polymorphism and aggression in SCZ patients. It is plausible that the discrepancy in the association between *BDNF* and aggression might depend on the lack of uniformity in the phenotypic definition of aggression. Indeed, less stringent definitions of aggression, together with inadequately powered sample size, might decrease the probability of identifying statistically significant association signals.

Recently, Dong et al. (2012) reported on two putatively functional polymorphisms within the methylenetetrahydrofolate reductase (*MTHFR*) gene, showing that T-allele polymorphism of rs1801133 and a T-C haplotype with rs1801131 were associated with aggressive behavior in Han Chinese SCZ patients. Finally, Su et al. (2015) analyzed the role of neurogranin (*NRGN*) gene as a risk factor for SCZ, as well as for aggressive behavior, showing that the CC genotype of the rs12807809 polymorphism was associated with a higher Positive and Negative Syndrome Scale (PANSS) aggression subscale score compared to the other genotypes. Taken together, these findings suggest that aggressive behavior in SCZ might be modulated by the presence of

Table 3Genetic studies of catechol-*O*-methyltransferase (*COMT*) in severe mental illness.

Severe mental illness	Polymorphism	Type of genotype-phenotype association	Reference
Schizophrenia	rs4680 (Val158Met), rs737865, rs165599 rs4680 (Val158Met) rs4680 (Val158Met)	Haplotypic association (A-A-G) with aggressive SCZ patients Met/Met genotypes were more aggressive than Val/Val and Val/Met carriers No association with aggression	(Gu et al., 2009) (Tosato et al., 2011) (Mohamed et al., 2015)
Borderline personality disorder	rs4680 (Val158Met)	Impulsive aggression was lower in Val/Val carriers who underwent serious life events	(Wagner et al., 2010)
ADHD	rs6269 (<i>COMT</i> promoter), rs4633 (His62His), rs4818 (Leu136Leu), and rs4680 (Val158Met) rs4680 (Val158Met)	Association between child aggression and two markers in <i>COMT</i> , rs6269, and rs4818 <i>COMT</i> Val allele carriers showed poorer response inhibition and set shifting abilities, reduced fear empathy and reduced autonomic responsiveness to the conditioned aversive stimulus, all traits predisposing to aggression	(van Goozen et al., 2016)
Alcohol dependence	rs4680 (Val158Met)	No association of rs4680 with a history of aggression	(Soyka et al., 2015)

ADHD: Attention-deficit/Hyperactivity disorder; SCZ: schizophrenia; *COMT*: catechol-*O*-methyltransferase.

specific genetic fingerprints influencing the homeostasis of neurobiological pathways involved in behavioral control. However, given the inherent limitations of the evidence presented above (inadequate sample size to decrease the probability of Type 1 error, heterogeneity in assessment of aggressive behavior, and absence of hypothesis free approach), the clinical applicability of these results appears unlikely, unless confirmed in future GWAS.

2.2. Bipolar disorder

Differently from SCZ, some genome-wide studies have explored the role of genetic variation in modulating aggressive behavior in BD (Doyle et al., 2010; Alliey-Rodriguez et al., 2011; Barzman et al., 2014) (Table 2). Using a sample of 765 individuals from 154 families enrolled in a linkage study of ADHD, Doyle et al. (2010) analyzed whether specific sets of markers were associated with the Juvenile Bipolar Disorder (JBD) phenotype determined by the sum of the scales on Attention Problems, Aggressive Behavior and Anxious/Depressed scales of the Child Behavior Checklist (CBCL). The heritability of the CBCL-JBD phenotype was substantial (0.71), and some chromosomal regions, 1p21.1, 6p21.3, and 8q21.13 surpassed the threshold for suggestive linkage (Doyle et al., 2010). These same regions were previously identified in molecular genetic studies of BD, SCZ, and ASD.

In the attempt of identifying genetic determinants of risk for BD using personality traits as endophenotypes, Alliey-Rodriguez et al. (2011) studied 944 BD individuals characterized with the Cloninger's Temperament and Character Inventory (TCI) and the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). The authors found an association signal, although not genome-wide significant, with the ZKPQ Aggressiveness-Hostility scale at the rs17190927 in the serine palmitoyltransferase, long-chain base subunit 3 (*SPTLC3*) gene (Alliey-Rodriguez et al., 2011). Finally, Barzman et al. (2014) studied the expression of tumor necrosis factor- α (*TNF α*) genes in relation to aggressive behavior as assessed by the Brief Rating of Aggression by Children and Adolescents (BRACHA) in ten adolescents with diagnosis of BD type 1. They found that three *TNF* gene expressions were inversely correlated with the BRACHA score while the mRNA levels of one *TNF* gene (*TNFAIP3*) was positively correlated with BRACHA score. In summary, these data point to genetic variants predisposing to aggressive behavior in BD. If replicated in further molecular genetic studies, these genes might be implemented in predictive models of aggressive behavior in BD.

2.3. Autism spectrum disorder

Despite the vast amount of molecular genetic data on ASD, and the relatively high prevalence of externalizing behavior in this spectrum of conditions, there is paucity of data on genetic predictors of aggressiveness in ASD. Using a standard candidate gene approach, Schuch et al. (2014) investigated 5 polymorphisms within the $\beta 3$ integrin (*ITGB3*) gene in a sample of 209 ASD children and their parents. The authors reported a nominal association of rs5918 TT genotype with symptoms of aggression (Schuch et al., 2014) (Table 1). Interestingly, a recent large collaborative study put together a large copy number variation (CNV) morbidity map of individuals with intellectual disability, developmental delay and/or ASD (Coe et al., 2014). By integrating these data with available public exome sequencing data, and by resequencing candidate genes in subjects with unexplained developmental delay, the authors were able to identify structural DNA mutations (truncations) of zinc-finger MYND domain 11 (*ZMYND11*) gene in individuals with ASD, aggression and complex neuropsychiatric features (Coe et al., 2014) (Table 2). The latter study is a testament that integrative molecular approaches combining CNV dataset with next-generation sequencing in large and accurately phenotyped samples, might pave the path toward the identification of reliable genetic determinants of risk for ASD, which might also modulate a shared susceptibility to

aggressive behavior.

2.4. Attention-deficit/hyperactivity disorder

As in other complex psychiatric disorders, only recently researchers have focused on genome-wide approaches to identify genetic signatures for aggressive behavior in ADHD. Hamshere and coauthors investigated whether ADHD polygenic risk scores derived from the largest GWAS meta-analysis could be enriched in an independent sample of ADHD patients with comorbid conduct disorder (Hamshere et al., 2013). Of note, the association of ADHD polygenic risk score with total conduct disorder score, was mainly driven by the increase in the number of aggressive conduct disorder symptoms, rather than of covert conduct disorder symptoms (Hamshere et al., 2013). Interestingly, another group investigated the genetic underpinning of oppositional defiant disorder, a common antecedent of aggressive behavior in ADHD, in a sample of 750 ADHD subjects (Aebi et al., 2016). They did not find any genome-wide significant association signal, although the top findings obtained from the GWAS (Table 2) fitted into a neurite outgrowth-regulating molecular pathway (Aebi et al., 2016). Finally, Brevik et al. (2016) performed a GWAS of 1060 adult ADHD patients assessed for aggressiveness using the Wender Utah Rating Scale (WURS). Subsequently, the authors performed enrichment of the GWAS top signals in the adult ADHD sample among genome-wide association signals of dimensions of oppositionality (defiant/vindictive and irritable dimensions) in childhood ADHD ($n = 750$). Although no single polymorphism reached genome-wide significance, the strongest signal in adult ADHD was observed at rs10826548, within a long noncoding RNA gene, closely followed by rs35974940 in the neurotrimin (*NTM*) gene (Brevik et al., 2016). Furthermore, the top association hits observed in adult ADHD showed significant enrichment of signals from both the defiant/vindictive dimension and the irritable dimension in childhood ADHD (Brevik et al., 2016).

3. Epigenetic of aggression in psychiatric disorders

As mentioned previously the investigation of epigenetic determinants of aggressive behavior stems from the evidence that shared environment appears to account for up to 20% of the phenotypic variation in aggression (Porsch et al., 2016). Indeed, disruptive behaviors, including overt aggression, appear to follow specific longitudinal developmental trajectories and typically start in early childhood (Tremblay, 2010). The impact of the identified risk factor for disruptive behavior (mainly mothers' poor social adjustment and lifestyle during pregnancy) on the genetic liability threshold for aggressive behavior appears to be mediated by the epigenetic machinery, which would modulate the activation (or inactivation) of the expression of genes (Tremblay, 2010; Tremblay and Szyf, 2010). Although no study has assessed the role of epigenetic variation in a specific SMI, it might be useful to briefly summarize the most recent evidence on conduct and antisocial disorders, as these disorders can increase the risk of aggressiveness, and might antecede, or present in comorbidity, with SMI, as in the case of ADHD or SCZ, respectively. Wang et al. (2012) found that adult males with high childhood-limited aggression had higher levels of methylation of *SLC6A4* gene promoter in both T cells and monocytes. Interestingly, in both cell types the methylation state of *SLC6A4* gene was associated with lower in vivo measures of brain 5-HT synthesis in the left and right lateral orbitofrontal cortex (Wang et al., 2012). Consistently, adult women who were found to be on a chronic physical aggression trajectory between 6 and 12 years of age had genome-wide signatures of DNA methylation in peripheral T cells distinct from those of adult women who followed a normal physical aggression trajectory (Guillemin et al., 2014).

Concerning antisocial personality disorder, Checknita et al. (2015) found in 86 incarcerated individuals a hypermethylation of *MAOA* promoter gene compared to healthy controls, possibly determining a

down-regulation of MAOA gene expression, and the consequent alteration of the monoaminergic homeostasis in the CNS. Indeed, the link between MAOA and aggression appears strong, although there is still uncertainty on the precise mechanistic process underlying this relationship (Godar et al., 2016). In summary, molecular epigenetic data show clearly that environmental moderators act on the predisposing liability threshold set by genetic factors altering the expression of specific genes through, but not exclusively, changes in DNA methylation.

4. Metabolomics of aggression in psychiatric disorders

Metabolomics allows the extensive profiling of the set of small molecules produced by cells offering a direct signature of biochemical activity (Patti et al., 2012). As such, this approach might be useful in identifying specific metabolic fingerprints of aggression in individuals with SMI. Differently from genomics, where the correlation between gene and phenotype is often based on probabilistic models, particularly in complex traits, metabolomics produces a specific biochemical signature directly linked to the phenotype under investigation. Metabolomics data, if analyzed jointly with genetic and epigenetic information, might produce prediction risk models with higher specificity and sensitivity of those including genetic and epigenetic data alone. This is particularly true for aggressive behavior where metabolomics might help identifying specific risk profiles, particularly in SMI as shown in a recent extensive review from Hagenbeek et al. (2016). In this section we focus mainly on ASD, since the clinical manifestation of this severe psychiatric disorder is often characterized by aggressive behavior. These results are summarized in Table 4.

Table 4
Metabolomics findings in autism spectrum disorder.

Type of sample	Method	Results	Reference
Urine	NMR	Perturbation in the tryptophan-nicotinic acid metabolic pathway and altered levels of taurine and glutamate, NAG, succinate	(Yap et al., 2010)
Urine	LC/GC-MS	Amino acid metabolism, increased oxidative stress, and mammalian microbial co-metabolism altered in ASD patients	(Ming et al., 2012)
Urine	NMR	β -alanine, glycine, taurine and succinate concentrations were significantly higher, and creatine and 3-methylhistidine concentrations were lower in ASD than in controls	(Mavel et al., 2013)
Urine	GC-MS	Higher urinary levels of succinate and glycolate, but lower levels of hippurate, 3-hydroxyphenylacetate, vanillylhydracrylate, 3-hydroxyhippurate, 4-hydroxyphenyl-2-hydroxyacetate, ¹ H-indole-3-acetate, phosphate, palmitate, stearate, and 3-methyladipate, than healthy children	(Emond et al., 2013)
Volatile urinary compounds	GC-MS	3-methyl-cyclopentanone, 3-methyl-butanal, 2-methyl-butanal, and hexane under acid conditions, and 2-methyl-pyrazine, 2,3-dimethyl-pyrazine, and isoxazolo under alkaline pH had statistically higher levels in urine samples from ASD children than from the control group	(Cozzolino et al., 2014)
Urine	GC-MS	ASD children had increased levels of 3-(3-hydroxyphenyl)-3-hydroxypropanoic acid, 3,4-dihydroxybutyric acid, glycolic acid and glycine, cis-aconitic acid, as well as phenylalanine, tyrosine, <i>p</i> -hydroxyphenylacetic acid, and homovanillic acid	(Noto et al., 2014)
Urine	NMR and HSQC NMR	The combination of NMR and HSQC NMR led to more accurate discrimination between ASD and healthy controls than the use of ¹ H NMR alone. Urinary excretion of succinate, glutamate and 3-methyl-histidine differed significantly between ASD and healthy control samples	(Nadal-Desbarats et al., 2014)
Urine	NMR and HSQC NMR/LC-HRMS (ESI + and ESI - on HILIC and C18 chromatography column)	Substantial predictive power of metabolite panel using six different techniques (AUC = 0.91); indoxyl sulfate, <i>N</i> - α -acetyl-L-arginine, methyl guanidine, and phenylacetylglutamine differed between ASD and healthy controls	(Dieme et al., 2015)
Plasma	GC-MS and LC-HRMS	1) decreased citric acid and increased succinic acid, 2) decreased fatty acids, including methylhexa-, tetra- and hepta-decanoic acids, 3) increased 3-aminoisobutyric acid, and 4) decreased creatinine	(West et al., 2014)
Serum	UPLC/Q-TOF MS/MS	Sphingosine 1-phosphate and docosahexaenoic acid associated with ASD	(Wang et al., 2016)

TRP: tryptophan; LCECA: high-pressure liquid chromatography coupled with electrochemical coulometric array detection; GC \times GC-TOF MS: two-dimensional gas chromatography coupled to time-of-flight mass spectroscopy; GC: gas chromatography; GC-MS: gas chromatography - mass spectrometry; LC-MS: Liquid chromatography-mass spectrometry; PBMC: peripheral blood; HPLC: High-performance liquid chromatography; AP: antipsychotic; LC-QTOF-MS: liquid chromatography coupled to a quadrupole time-of-flight mass spectrometer; NMR: nuclear magnetic resonance; BD: bipolar disorder; CSF: cerebrospinal fluid; CE-TOF MS: capillary electrophoresis time-of-flight mass spectrometry; ASD: autism spectrum disorder; HSQC: ¹H-¹³C heteronuclear single quantum coherence; LC-HRMS: liquid chromatography - high-resolution mass spectrometry; ESI +: positive electrospray ionization; ESI -: negative electrospray ionization; AUC: are aunder curve; UPLC/Q-TOF MS/MS: ultra-performance liquid chromatography quadrupole time-of-flight tandem mass spectrometry.

4.1. Autism spectrum disorder

Most of the evidence on metabolomics of ASD comes from the analysis of urinary samples. Indeed, using ¹H nuclear magnetic resonance (NMR) spectroscopy in urine samples, Yap et al. (2010) found that ASD patients showed increased urinary excretion of *N*-methyl-2-pyridone-5-carboxamide, *N*-methyl nicotinic acid, and *N*-methyl nicotinamide indicating a perturbation in the tryptophan-nicotinic acid metabolic pathway. In addition, amino acids such as taurine and glutamate, NAG, succinate, were consistently altered in the ASD group compared to controls (Yap et al., 2010). Subsequently, Ming et al. (2012) found that urinary specimens of ASD patients had substantial perturbation of the metabolomic profile, including amino acid metabolism, increased oxidative stress, and mammalian microbial co-metabolism, compared to age matched healthy controls. Another study using ¹H NMR spectroscopy found that metabolomic profiling of urine samples discriminated effectively controls from ASD patients, with the latter showing higher levels of β -alanine, glycine, taurine and succinate concentrations, and lower levels of creatine and 3-methylhistidine (Mavel et al., 2013).

Further, urinary metabolomics profiling of 26 ASD and 24 healthy children showed substantial differences, with ASD patients presenting higher urinary levels of succinate and glycolate, but lower levels of hippurate, 3-hydroxyphenylacetate, vanillylhydracrylate, 3-hydroxyhippurate, 4-hydroxyphenyl-2-hydroxyacetate, ¹H-indole-3-acetate, phosphate, palmitate, stearate, and 3-methyladipate, than healthy children (Emond et al., 2013). Cozzolino et al. (2014) focused instead on metabolomics of volatile urinary compounds, studying samples under both acid and alkaline pH to detect metabolites specific of each physicochemical condition. They showed that 3-methyl-cyclopenta-

none, 3-methyl-butanol, 2-methyl-butanol, and hexane under acid conditions, and 2-methyl-pyrazine, 2,3-dimethyl-pyrazine, and isoxazolo under alkaline pH had statistically higher levels in urine samples from ASD children than from the control group (Cozzolino et al., 2014). Comparing urine samples of 21 ASD children with 21 age-matched healthy controls, Noto et al. (2014) found distinct metabolomics profile discriminating with relatively good accuracy the two groups. Specifically, they found that ASD children had increased levels of 3-(3-hydroxyphenyl)-3-hydroxypropanoic acid, 3,4-dihydroxybutyric acid, glycolic acid and glycine, cis-aconitic acid, as well as phenylalanine, tyrosine, *p*-hydroxyphenylacetic acid, and homovanillic acid (Noto et al., 2014).

Interestingly, Nadal-Desbarats et al. (2014) investigated whether, by combining two approaches for metabolomics profiling, ^1H NMR and ^1H - ^{13}C heteronuclear single quantum coherence (HSQC), it was possible to detect more reliably metabolites profiles in urinary specimens from ASD patients. Indeed, they found that the combination of the two approaches led to more accurate discrimination between ASD and healthy controls than the use of ^1H NMR alone. Urinary excretion of succinate, glutamate and 3-methyl-histidine differed significantly between ASD and healthy control samples (Nadal-Desbarats et al., 2014). Finally, another study in urinary specimens confirmed the importance of using combined techniques for metabolomics profiling (Dieme et al., 2015). Using different approaches [^1H NMR, ^1H – ^{13}C HSQC NMR, and liquid chromatography – high-resolution mass spectrometry in positive and negative electrospray ionization (ESI+ and ESI–) modes] the authors obtained a panel of metabolites with a substantially high predictive power [Area Under Curve (AUC) = 0.91]. Metabolites that were most significantly different between ASD and control children were indoxyl sulfate, *N*- α -acetyl-L-arginine, methyl guanidine, and phenylacetylglutamine.

Finally two studies performed metabolomics profiling in peripheral plasma (West et al., 2014) and serum (Wang et al., 2016). West et al. (2014) showed that plasma metabolomics fingerprints of ASD patients differed substantially from those of healthy subjects, confirming previous results of ASD-associate markers, such as 1) tricarboxylic acid cycle associated molecules including citric acid (decreased) and succinic acid (increased), 2) decreased fatty acids, including methylhexa-, tetra- and hepta-decanoic acids, 3) increased 3-aminoisobutyric acid, and 4) decreased creatinine. The study by Wang et al. (2016) used two large case/control cohorts to identify and validate metabolomics profiles in ASD. They showed that autism was consistently associated with 2 particular metabolites: sphingosine 1-phosphate and docosahexaenoic acid, which could be reliable biomarkers of illness status in ASD.

5. Microbiomics and aggression in psychiatric disorders

As previously discussed, it is plausible that an additional component, gut microbiota, might play a role in modulating the susceptibility toward aggression. Although this hypothesis has not been formally tested in human studies, evidence from animal studies renders plausible the link between alterations of gut microbiota and aggressiveness (Rohrscheib et al., 2015). Indeed, researchers found that *Wolbachia* bacteria, endosymbionts of numerous insect species, might determine aggressive behavior in *Drosophila melanogaster*, when they infect the brain of flies through gut contamination (Rohrscheib et al., 2015). It is well established that microbiota might influence several physiological components of the gut-brain axis, inducing increased anxiety and depressive-like behaviors as well as increased stress reactivity (Foster and McVey Neufeld, 2013), often proxies of aggressive behavior. Gut microbiota might also modulate tryptophan metabolism in the host by decreasing the fraction available for serotonin synthesis and increasing the production of neuroactive metabolites through the kynurenine pathway (O'Mahony et al., 2015). Furthermore, the modification of gut microbiome through the use of probiotics in animal models might influence behavior, reducing for instance stress reactivity (Ohland

et al., 2013; Foster et al., 2016).

Human metabolomics studies in ASD have supported, albeit indirectly, the hypothesis of a link between gut microbiota and aggression (Ming et al., 2012; Noto et al., 2014; Yap et al., 2010). In fact, profiling of ASD patients has shown perturbation in sulfur and amino acid metabolism (Yap et al., 2010), carbohydrates, and bile acids (Ming et al., 2012), and 4-hydroxyhippuric acid (Noto et al., 2014), all pathways related to alterations in the gut microbiota of ASD subjects. Interestingly, when Ming et al. (2012) analyzed metabolomics profile in ASD children with and without gastrointestinal dysfunction symptoms separately, the ASD children with gastrointestinal dysfunction symptoms had significantly altered gut microbiome metabolites, whereas ASD children without gastrointestinal dysfunction symptoms exhibited similar gut bacterial metabolite profiles to controls.

In summary, interpretation of these data offers at least two plausible connections between gut microbiota and aggressiveness. First, several neurochemical pathways underlying aggression appear to be modulated by gut microbiota. Second, these perturbations, detected through metabolomics, have been detected in ASD individuals who often manifest externalizing behaviors of severe entity.

6. Summary

Aggression is a complex phenotype, particularly when evaluated in the context of SMI. This complexity is determined primarily by its multifactorial pathogenesis, but also by the inherent difficulty in obtaining a uniform phenotypic definition. Further, this phenotypic and pathophysiological heterogeneity appears to have hindered the advancement in the identification of reliable biological predictors of aggression. In our review, we described several genetic and epigenetic markers that might be tested in predictive models of aggressive behavior in SMI patients. However, it should be noted that, to be suitable for inclusion in such models, markers should be prioritized on the basis of: 1) presence of replicated findings in independent studies, and 2) data from hypothesis-free *epi*/genome-wide approaches. Currently, only findings from GWAS, particularly in BD and ADHD, might warrant further analytical steps in predictive models.

The same theoretical approach should be applied for metabolomic findings. However, compared to genetic and epigenetic data, biochemical signatures in SMI show more consistent patterns across studies, as, for instance, pathways regulating redox reactions in SCZ, glutamic acid in BD, and hippurate in ASD, making them more likely to be reliable candidate for being tested in predictive models. On the other hand, a relevant limitation is the absence of studies directly investigating aggressive behavior phenotype, which, as described previously, might be relatively heterogeneous in SMI (physical or verbal, self- or hetero-directed). Interestingly, metabolomics evidence in SMI, particularly in ASD, has pointed to possible alterations of gut microbiota as one of the pathophysiological determinant of aggressiveness, showing also the heuristic validity of this analytical approach.

7. Future directions

The increasing evidence that specific alterations of gut microbiome might determine changes in CNS signaling pathways highlights the key role of one environmental moderator often underestimated in current biological psychiatry research: diet. It is plausible that in the presence of a genetic predisposition the interaction of a certain kind of diet with a specific type of intestinal microbiota might produce metabolites that pass into the bloodstream and could modulate the structure and function of our organs, including the brain. It is known that many illnesses derive from an imbalance induced by an inappropriate diet that leads to dysbiosis, that is, the abnormal colonization by an intestinal bacterial species that outweighs the others. Not dissimilarly this might happen in SMI as it has been suggested for ASD, where *Clostridium* spp. might play a role. The intestinal microbiota interacts

with the immune system and orients it. These forces are at work throughout our lives, but they are of the utmost importance during time windows when our development, both fetal and in the first years of our lives, is at risk. We must underline that in the first 3 years the brain, the immune system, and the microbiome are established. In the next years preventive measures will probably be available in rebalancing the intestinal microbiota with prebiotics, probiotics, and symbiotics (prebiotics + probiotics), as well as with the transplant of intestinal microbiota with bacteria from healthy subjects. The most important question to be answered today is “what is a normal microbiota?” A new class of probiotics defined psychobiotics will, at least partially, replace some traditional treatments (Zhou and Foster, 2015). Nutrition, especially in vulnerable period of growth, will reach an outstanding importance in prevention and co-treatment of mental illness.

Clearly, only the integration of several level of information (clinical, genetic, epigenetic, proteomic, metabolomic and so on) will lead to the precise understanding of the neurobiological underpinnings of aggression. In keeping with this approach, a recent study indicated that only the integration of several factors (biological and psychopathological) helped dissecting the clinical heterogeneity of aggression and led to the development of a reliable framework for the identification of neurobiological determinants of aggression (Comai et al., 2016). This is also indirectly confirmed by the fact that current and most active psychopharmacological therapies for aggression such as atypical antipsychotics and mood stabilizers act on multiple extra- and intra-cellular as well as genetic targets (Comai et al., 2012; Brodie et al., 2016).

The application of holistic technologies such as metabolomics and microbiomics will provide an image of the incredible complexity of every individual and capture his or her distinct and unique metabolic fingerprint as well as the longitudinal transitioning of biochemical pathways from a state of health to one of illness and from the latter to recovery or improvement.

Genomic studies have been applied for years to SMI. Today, these technologies remain extremely complex, costly, and inaccessible to most of the population. But it is not difficult to foresee an explosion in research on “omics” applications in the next 5 years, which will lead to the production of simple, affordable, and ergonomic instruments, such as, for instance, kits for the metabolomic analysis of urine in different pathologies of the brain. This will take us from pure research to the patient's bedside, thus providing an example of translational research.

To this end, several European researchers have joined forces to perform a large scale study which makes use of genomic, epigenomic, and metabolomic to disentangle the heterogeneity of aggression and highlight pathways from molecule to phenotype (Boomsma, 2015). This project, funded by the European Union (ACTION: Aggression in Children: Unraveling gene-environment interplay to inform Treatment and Intervention strategies) sees the contribution of twelve partners from the Scandinavian countries (Finland and Sweden), the UK, the Netherlands, and Italy together with scientists from the USA and Australia. After discovery of putative biomarkers in population samples, these findings will be validated in clinical cohorts and the results of the ACTION consortium will provide the basis for an overarching model that integrates the multilevel empirical findings into a comprehensive framework of aggression and its risk indicators.

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Author contribution

MM and VF both contributed to this review by searching and

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed in the acknowledgement.

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