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Discovery of Biochemical Biomarkers for Aggression: A Role for Metabolomics in Psychiatry

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Human aggression encompasses a wide range of behaviors and is related to many psychiatric disorders. We introduce the different classification systems of aggression and related disorders as a basis for discussing biochemical biomarkers and then present an overview of studies in humans (published between 1990 and 2015) that reported statistically significant associations of biochemical biomarkers with aggression, DSM-IV disorders involving aggression, and their subtypes. The markers are of different types, including inflammation markers, neurotransmitters, lipoproteins, and hormones from various classes. Most studies focused on only a limited portfolio of biomarkers, frequently a specific class only. When integrating the data, it is clear that compounds from several biological pathways have been found to be associated with aggressive behavior, indicating complexity and the need for a broad approach. In the second part of the paper, using examples from the aggression literature and psychiatric metabolomics studies, we argue that a better understanding of aggression would benefit from a more holistic approach such as provided by metabolomics.

Key words: aggression; biomarkers; psychiatry; metabolomics

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INTRODUCTION

Arguably, "violence and aggression are the most serious problems facing humanity" [Chichinadze et al., 2011]. One approach in the study of aggression and its etiology is at a biochemical level. Biochemical markers are intermediate to the outward phenotype and the underlying biology of aggression. They can aid in elucidating the causes and (patho) physiology of aggressive behavior [James et al., 2006; Scoriels et al., 2015]. One of the promises of

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biochemical studies of central nervous system diseases is the development of biochemically based biomarkers [Kaddurah-Daouk and Krishnan, 2009]. Biomarkers can be applied in diagnosis, in assessment of disease stages, as indicators of disease prognosis, and for prediction or monitoring of interventions and treatment responses. Some biomarkers are "surrogate endpoints" which substitute clinical endpoints that reflect "how a patient feels, functions, or survives" [Atkinson et al., 2001]. There are several comprehensive overviews of biochemical compounds as potential biomarkers for aggression [e.g., Siever, 2008; Yanowitch and Coccaro, 2011], including reviews of neurotransmitters [e.g., de Almeida et al., 2005; Seo et al., 2008; Siever, 2008; Wallner and Machatschke, 2009; Chichinadze et al., 2011; Yanowitch and Coccaro, 2011; Haller, 2013; Umukoro et al., 2013; Morrison and Melloni, 2014; Narvaes and Almeida, 2014; Willner, 2015], hormonal networks [Simpson and Hons, 2001; Wingfield et al., 2006; Siever, 2008; Soma et al., 2008; Chichinadze et al., 2011; Eisenegger et al., 2011; Haller, 2014a,c; Soma et al., 2015], and cytokines [e.g., Zalcman and Siegel, 2006]. With a few exceptions [e.g., Siever, 2008], these reviews focus on a single biochemical class, studying biomarkers belonging to various different biochemical pathways in isolation. This makes it more difficult to draw substantive conclusions about aggression on a biochemical network or "systems biology" level. A systems biological description of aggression would be particularly useful, although "metabolic snapshots" (as provided for instance by metabolic profiling of a single sample from each individual participating in a molecular epidemiological study) are insufficient to reconstruct models of the metabolic network underlying this phenotype [Kell, 2004]. Further progress in aggression research might benefit from a more "holistic" approach, where biochemical markers from a wide variety of biochemical classes are studied simultaneously. One such a holistic approach is by metabolomics, the comprehensive study of all metabolites in a given sample. A metabolomics approach might allow for the discovery of novel biomarkers of aggression and its subtypes for increasing insight into the biochemical mechanisms of aggression, and consequently to identify new drug targets [Kaddurah-Daouk and Krishnan, 2009].

This article consists of two parts. In the first part, we present a review of studies that aimed at the evaluation and discovery of biochemical biomarkers for aggression, aggression-related disorders, and for distinct aggression subtypes. We start with a short overview of classification systems for aggression and then present an overview of research into biochemical biomarkers for aggression for disorders of which aggression is a component, and for its subtypes. In the second part of the article, we discuss the role metabolomics can play in the quest for biochemical biomarkers of aggression.

AGGRESSION CLASSIFICATIONS

Aggression is a heterogeneous concept that is commonly defined as "hostile, injurious, or destructive behavior" [Siever, 2008], but for which many alternative definitions, subtypes and classification systems have been suggested [Weinshenker and Siegel, 2002; Ramírez and Andreu, 2003; Vitaro et al., 2006; Ramírez, 2009, 2011]. Human aggressive behavior encompasses a wide range of behaviors and occurs in multiple contexts. Subtypes of aggression have been classified by the mode of aggression, target (self, other, objects), and cause/function. Supplementary Table SI lists the different subtypes as they apply to each of the different forms of classification systems. Based on the target of aggression, a distinction is made between direct and indirect aggression. Direct aggression can encompass both physical and verbal aggression as long as there is a direct confrontation between an aggressor and a target. Indirect aggression is characterized by a lack of direct confrontation; examples of indirect aggression include social manipulations and secretly damaging property [Collett et al., 2003]. Direct or indirect aggression can be further distinguished by the modes of aggression, that is, both can be physical or verbal, which is sometimes denoted as relational aggression. Sometimes an argument is made for adding a third subtype referring to nonverbal behavior or body language, such as facial expressions [Ramírez and Andreu, 2003].

Next, all types of aggression can be classified following the functional aspect of aggressive behavior (see Supplementary Table SI). It has been argued that the differences among the functional classification systems are semantic in nature and that different fields of study refer to the same kind of aggression under different names [Weinshenker and Siegel, 2002]. Therefore, Ramírez and Andreu [2006] and Ramírez [2009, 2011] proposed a single dichotomous system including a "social-cognitive subtype" and an "emotional subtype" of aggression. The first subtype is goal-oriented and is associated with a positive evaluation of aggression. It encompasses the instrumental [purposeful and goal-oriented; McEllistrem, 2004], proactive [aimed at securing resources or dominion; Vitaro et al., 2006], and premeditated [planned goal-oriented; Ramírez, 2009] forms of aggression, including behaviors such as "controlling others" and "habitual lying". The second subtype is uncontrolled aggressive behavior and includes the hostile ["intent to harm another person"; Ramírez and Andreu, 2003], reactive [response to a perceived threat or provocation; Vitaro et al., 2006], and impulsive [aimed at gratification without concern for consequences; Ramírez, 2009] subtypes of aggression, which includes behaviors such as "getting angry" and "starting fights" [Ramírez and Andreu, 2006; Ramírez, 2009, 2011].

The Diagnostic and Statistical Manual for mental disorders [DSM-IV; American Psychiatric Association, 2000] recognizes psychiatric disorders in children and adults in which aggression is one of the characterizing symptoms. In children, oppositional defiant disorder (ODD) is characterized by negative, defiant, disobedient, and hostile behavior toward authority figures, while conduct disorder (CD) encompasses a behavior pattern marked by violations of the basic rights of others and of societal norms and rules [Loeber et al., 2000]. CD is mainly characterized by physical and relational aggression, and ODD by anger [Haller, 2014b]. Proactive aggression during childhood is a risk factor for the development of delinquent behavior, ODD, and CD during adolescence [Vitaro et al., 1998]. In adults intermittent explosive disorder (IED), borderline personality disorder (BPD) and antisocial personality disorder (APD) each have aggression or an aggression-related phenotype (e.g., impulsivity, hostility, anger [Ramírez and Andreu, 2006]) as potential symptoms. Patients meeting criteria for IED suffer from multiple episodes of

disproportionate impulsive aggression [Coccaro, 2012], whereas patients diagnosed with one of the other disorders are not necessarily aggressive: individuals can be diagnosed with one of these disorders without presenting aggressive tendencies [Haller, 2014b]. APD is characterized by a pattern of persistent antisocial behavior and is preceded by conduct problems evident before age 15 [Hare et al., 1991]. APD is associated with physical aggression, irritability, and impulsivity. BPD is characterized by emotional dysregulation, which often manifests as impulsive, self-destructive, or (predominantly self-directed) aggressive behavior [Siever, 2008; Scott et al., 2014]. Other psychiatric disorders, such as autism [Farmer and Aman, 2011; Farmer et al., 2015] or schizophrenia [Weiss, 2012; Bo et al., 2014], are also associated with aggression, but aggression is not one of the criteria required for the DSM-IV diagnosis.

AGGRESSION BIOCHEMISTRY

An overview of studies (published between 1990 and 2015) focusing on putative biochemical biomarkers for aggression subtypes, disorders of which aggression is a (potential) symptom, or overall aggression in humans is given in a set of (supplementary) tables. Table I summarizes the biomarkers reported for total aggression scores, which often are based on assessments by questionnaires. Table II gives an overview of the biomarkers reported for DSM-IV disorders as discussed above, and Table III summarizes the biomarkers reported for the aggression classification systems per subtype. More details are provided in Supplementary Tables SII–IV, indicating for each study in which a significant association of aggression with at least one biochemical biomarker was found in which population the study was conducted; the assayed biofluid; whether the association(s) of the metabolite(s) or enzyme(s) with aggression was (were) positive or negative; and the main conclusions reached by the authors based on the study findings. All tables contain measures of aggression assessed in population and clinical samples, and report significant associations only. Reviews of potential biochemical biomarkers of aggression often focus on a particular class of metabolites. In contrast, in Table I, we list all studies focusing on potential biomarkers for aggression across all classes of biochemicals, ordering the studies by type of aggression measure rather than by biochemical class. As can be seen in this table, markers from various classes have been observed to associate with each of the different aggression measures. Consistent with a review on the role of cytokines in aggression [Zalcman and Siegel, 2006], we observed several studies indicating an increase in inflammation marker (IL-6, CRP) levels in relation to aggression, in both adolescents and adults using different aggression measures [Coccaro, 2006, 2014; Holtmann et al., 2013]. Increased levels of C-reactive protein and interleukin-6 have also been observed in patients with IED [Table II; Coccaro et al., 2014], which seems to suggest that inflammation markers mainly play a role in impulsive aggression.

Investigations into neuroendocrine mechanisms underlying aggressive behavior have focused mainly on gonadal sex steroid hormones (e.g., testosterone, which is regulated by the hypothalamic–pituitary–gonadal axis [HPG]). As can be seen in Table I, increased levels of the HPG hormone testosterone are observed in aggressive adolescents [Yu and Shi, 2009] and adult males convicted for crimes [Horn et al., 2014]. In contrast, a decreased free testosterone index has been associated with CD in girls [Table II; Pajer et al., 2006]. Overall, meta-analyses revealed a weak positive relationship between testosterone and aggression [Archer, 1991; Book et al., 2001; Archer et al., 2005]. Conduct disorder and ODD have also been linked to other androgens (Table II). The testosterone precursor androstenedione and its precursor, dehydroepiandrosterone sulfate (DHEA-S), were elevated in boys with CD [van Goozen et al., 1998a]. Increases in DHEA-S levels have also been observed in a mixed sample of CD patients [Dmitrieva et al., 2001] and in children with ODD [van Goozen et al., 2000]. Another approach has been to investigate the role of the endocrine structures underlying the hypothalamic–pituitary–adrenal (HPA) axis, in order to evaluate the role of the stress response system in aggression [Barzman et al., 2010]. In humans, the most important stress hormone is cortisol as produced by the adrenal glands [Crowley and Girdler, 2014], and as can be seen throughout the tables this hormone was significantly associated with aggression in many studies. Low cortisol levels have been associated with high total aggression measures [Table I; van de Wiel et al., 2004; Yu and Shi, 2009; Poustka et al., 2010; Platje et al., 2013a,b; Horn et al., 2014; McBurnett et al., 2014], CD [Table II; Pajer et al., 2001; Oosterlaan et al., 2005], ODD [Table II; van Goozen et al., 1998b], and with reactive and proactive aggression [Table III; Poustka et al., 2010; Stoppelbein et al., 2014]. In contrast, increased levels of cortisol have also been observed for higher total aggression measures [Table I; Barzman et al., 2013], CD [Table II; van Bokhoven et al., 2005], and reactive aggression [Table III; van Bokhoven et al., 2005; Lopez-Duran et al., 2009]. While the results of studies that investigate the cortisol-aggression relationship are not conclusive, overall, decreased cortisol levels have been observed with higher aggression levels. Further evidence for a role of the stress response system in aggressive behavior comes from studies investigating saliva levels of the adrenergic stress response marker alpha-amylase [Nater et al., 2005]. An interaction effect for alpha-amylase and cortisol was observed, in which low cortisol level was only predictive for aggressive behavior for low alpha-amylase levels [Table I; Gordis et al., 2006].

The HPA and HPG axes are not isolated systems: DHEA is co-released from the adrenal glands together with cortisol and has anti-glucocorticoid effects [Crowley and Girdler, 2014]. This co-release of DHEA and cortisol occurs through stimulation of adrenocorticotropic hormone (ACTH; cortisol precursor) to the adrenal glands, stimulating DHEA synthesis [Crowley and Girdler, 2014]. In CD patients, an increase in ACTH has been observed [Table II; Dmitrieva et al., 2001], which would also explain the observed increase in DHEA(-S) levels in CD patients [van Goozen et al., 1998a, 2000; Dmitrieva et al., 2001]. Furthermore, a decrease in the ratio of cortisol to DHEA-S has been observed in girls with CD with respect to non-CD controls [Table II; Pajer et al., 2006], which might indicate that the majority of ACTH is used to stimulate DHEA synthesis and not used as a precursor for cortisol. The hormonal influences on aggressive behavior are complex and vastly interconnected, with other hormone classes than androgens and glucocorticoids also playing a role in aggression. The thyroid hormones triiodothyronine and thyroxin have both been associated with aggression. Low levels of free thyroxin have been

TABLE I. Significant Associations of Potential Biomarkers for Total Aggression Scores Based on Questionnaires

Population[a]	Questionnaire	Biomarker(s)[b]	References
69 IED patients 61 non-aggressive patients axis I/II disorder 67 controls	Composite Aggression Score (from multiple questionnaires)	Increased • IL-6 • CRP	Coccaro et al. [2014]
38 boys with disruptive behavior	Composite Aggression Score (from multiple questionnaires)	Decreased • Cortisol	McBurnett et al. [2014]
20 healthy volunteers 40 personality disorder subjects	Composite Aggression Score (from multiple questionnaires)	Increased • 5-HIAA Decreased • HVA	Coccaro and Lee [2010]
10 healthy volunteers 28 personality disorder subjects	Composite Aggression Score (from multiple questionnaires)	Increased • Glutamate	Coccaro et al. [2013]
99 subjects with personality disorders	Buss–Durkee Hostility Inventory	Increased • CRP	Coccaro [2006]
38 subjects with personality disorders	Buss–Durkee Hostility Inventory	Increased • Substance P-like immunoreactivity levels	Coccaro et al. [2012]
77 psychiatrically healthy adults	Buss–Durkee Hostility Inventory	Decreased • GABA	Bjork et al. [2001]
60 male subjects committed for serious criminal acts 66 male controls	Karolinska Scale of Personality	Increased • Free triiodothyronine Decreased • MAO • Free thyroxin	Stalenheim [2004]
67 adolescents from longitudinal study to effects of maltreatment	Reactive–Proactive Aggression Questionnaire	Decreased • α-amylase reactivity • Cortisol reactivity	Gordis et al. [2006]
20 aggressive adolescents 20 non-aggressive adolescents	Child Behaviour Checklist/ Youth Self-Report	Decreased • Cortisol Increased • Testosterone	Yu and Shi [2009]
425 adolescents	Child Behaviour Checklist/ Youth Self-Report	Decreased • Cortisol	Platje et al. [2013b]
390 adolescents	Child Behaviour Checklist/ Youth Self-Report	Decreased • Cortisol	Platje et al. [2013a]
22 children with disruptive behavior	Child Behaviour Checklist/ Youth Self-Report	Decreased • Cortisol	van de Wiel et al. [2004]
51 children and adolescents with a CBCL-DP 82 CBCL-DP control children and adolescents	Child Behaviour Checklist/ Youth Self-Report	Increased • CRP Decreased • Albumin	Holtmann et al. [2013]
Study 1 15 ODD boys 25 controls Study 2 22 ODD 25 controls	Child Behaviour Checklist/ Youth Self-Report	Decreased • 5-HIAA • HVA	van Goozen et al. [1999]

TABLE I. (*Continued*)

Population[a]	Questionnaire	Biomarker(s)[b]	References
40 healthy volunteers 20 aggressive subjects	Buss–Perry Aggression Questionnaire	Decreased • Apo A-I • Apo B • LDL-C • HDL-C • Apo A-I/Apo B ratio Increased • LDL-C	Troisi and D'Argenio [2006]
245 adolescents at risk for psychopathy	Buss–Perry Aggression Questionnaire	Decreased • Cortisol	Poustka et al. [2010]
17 psychiatrically hospitalized boys	Brief Ratings of Aggression by Children and Adolescents	Increased • Cortisol	Barzman et al. [2013]
29 children with disruptive behavior disorders 43 children with OCD	Modified Overt Aggression Scale	Decreased • 5-HIAA	Kruesi et al. [1990, 1992]
1995 participants from the HSCORE consortia	Cook–Medley Hostility Scale	Decreased • LDL-C	Sahebzamani et al. [2013]
545 newly convicted males	MacArthur Community Violence Instrument	Decreased • Cortisol Increased • Testosterone	Horn et al. [2014]
93 MDD patients	Life History Aggression	Decreased • 5-HIAA Increased • MHPG	Placidi et al. [2001]
26 subjects with personality disorder	Life History Aggression	Increased • Arginine vasopressin	Coccaro et al. [1998]

[a]Abbreviations as mentioned in the population column: IED, intermittent explosive disorder; CBCL-DP, child behavior checklist dysregulation profile; ODD, oppositional defiant disorder; OCD, obsessive compulsive disorder; MDD, major depressive disorder.
[b]Abbreviations as mentioned in the biomarker(s) column: IL–6, interleukin-6; CRP, C-reactive protein; 5-HIAA, 5-hydroxindoleacetic acid; HVA, homovanillic acid; GABA, gamma-amino butyric acid; MAO, monoamine oxidase; Apo-AI, apo lipoprotein AI; Apo-B, apo lipoprotein B; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; MHPG, 3-methoxy-4-hydroxyphenylglycol.

associated with total aggression in male convicts [Table I; Stalenheim, 2004], while increased levels of free triiodothyronine have been found in male convicts [Table I; Stalenheim, 2004] and CD patients [Table II; Dmitrieva et al., 2001]. However, only a small percentage of thyroid hormones travels unbound through the blood stream; one of the carriers of thyroid hormones is albumin, for which low levels have been associated with total aggression [Table I; Holtmann et al., 2013], which might suggest that when albumin levels are low the levels of circulating unbound triiodothyronine increase (associated with increased aggression).

Most major neurotransmitters are believed to play a role in aggressive behavior, with the serotonergic system responsible for the inhibition of aggressive behavior; the dopaminergic system responsible for the initiation of aggressive behavior; and the gamma-Aminobutyric acid-ergic (GABAergic) system responsible for appraising aggression-related cues [Willner, 2015]. Monoamine oxidase (MAO) catabolizes serotonin (5HT) into 5-hydroxyindolealdehyde (5-HIAL), which is then converted into 5-hydroxyindoleacetic acid (5-HIAA) by aldehyde dehydrogenase [Wong et al., 2005]. Both MAO levels and 5-HIAA are associated with total aggression (Table I). Decreases in the MAO levels have been observed in aggressive male criminals [Stalenheim, 2004] and low levels of 5-HIAA are associated with total aggression [Kruesi et al., 1990, 1992; van Goozen et al., 1999; Placidi et al., 2001], ODD [Table II; van Goozen et al., 1999], and physical aggression [Table III; Kruesi et al., 1992]. However, increased levels of 5-HIAA have also been observed for total aggression [Table I; Coccaro and Lee, 2010], and impulsive aggression [Table III; Coccaro and Lee, 2010]. The association of low 5-HIAA levels and aggression might be explained by reduced 5HT transport activity as observed in aggression [Siever, 2008] or by activation of the pre-synaptic 5HT 1_B receptor which inhibits 5HT release and thereby 5HT concentration [Sari, 2004]. Also, altered activation of 5HT receptors plays a role in aggression, including increased 5HT 1_A activation [de Almeida et al., 2005] and reduced 5HT 2_C activation [Siever, 2008].

Overall, disinhibition of (impulsive) aggressive behavior seems related to hypo-activity of the serotonergic system in the prefrontal cortex and anterior cingulate [de Almeida et al., 2005]. This hypoactivity also results in reduced control by serotonin of the dopamine system, leading to dopamine hyperactivity, thereby increasing aggressive behavior even further [Soderstrom et al., 2003; Seo

TABLE II. Significant Associations of Potential Biomarkers for the DSM-IV Disorders With Aggression as a (Potential) Characterizing Symptom

Disorder	Population[a]	Biomarker(s)[b]	References
Intermittent explosive disorder	69 IED patients 61 non-aggressive patients axis I/II disorder 67 controls	Increased • IL-6 • CRP	Coccaro et al. [2014]
Conduct disorder	194 boys from longitudinal population study	Increased • Cortisol	van Bokhoven et al. [2005]
Conduct disorder	28 CD patients 13 controls	Increased • ACTH Decreased • DHEA-S • Free triiodothyronine • IGF-I • IGFBP-3	Dmitrieva et al. [2001]
Conduct disorder	15 CD boys 25 control boys	Increased • DHEA-S • Androstenedione	van Goozen et al. [1998a]
Conduct disorder	250 male criminal offenders with APD	Decreased • Total cholesterol	Repo-Tiihonen et al. [2002]
Conduct disorder	47 girls with CD 36 control girls	Decreased • Cortisol to DHEA-S ratio • SHBG • Free testosterone index	Pajer et al. [2006]
Conduct disorder	47 girls with CD 37 control girls	Decreased • Cortisol	Pajer et al. [2001]
Conduct disorder	18 ODD/CD children 7 antisocial children without ODD/CD	Decreased • Cortisol	Oosterlaan et al. [2005]
Oppositional defiant disorder	21 ODD boys 31 control boys	Decreased • Cortisol	van Goozen et al. [1998b]
Oppositional defiant disorder	24 ODD children 42 psychiatric controls 30 normal controls	Increased • DHEA-S	van Goozen et al. [2000]
Oppositional defiant disorder	Study 1 15 ODD boys 25 controls Study 2 22 ODD 25 controls	Decreased • 5-HIAA • HVA	van Goozen et al. [1999]
Antisocial personality disorder	250 male criminal offenders with APD	Decreased • Total cholesterol	Repo-Tiihonen et al. [2002]

[a]Abbreviations as mentioned in the population column: IED, intermittent explosive disorder; CD, conduct disorder; ODD, oppositional defiant disorder; APD, antisocial personality disorder.
[b]Abbreviations as mentioned in the biomarker(s) column: IL–6, interleukin-6; CRP, C-reactive protein; ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulphate; IGF-I, insulin-like growth factor I; IGFBP–3, insulin-like growth factor binding protein 3; SHBG, sex hormone binding globulin; 5-HIAA, 5-hydroxindoleacetic acid; HVA, homovanillic acid.

et al., 2008). Interconnections between 5HT and dopamine are mediated through receptors which act both as autoreceptors (controlling activity of "own" neurotransmitter, for example, receptor from the serotonergic system controlling activity of serotonin) and heteroreceptors [controlling activity of "other" neurotransmitters, e.g., receptor from the serotonergic system controlling activity of dopamine; Hamon and Blier, 2013]. Serotonin influences the activity of the dopaminergic system through the 5HT 2_C receptor: activation of this receptor reduces dopamine release [de Deurwaerdère et al., 2004]. Increased levels of the dopamine breakdown product 3-methoxy-4-hydroxyphenylglycol (MHPG) have been associated with total aggression [Table I;

TABLE III. Significant Associations of Potential Biomarkers for the Aggression Subtypes From the Different Bimodal Classification Systems

Aggression subtype	Population[a]	Biomarker(s)[b]	References
Verbal aggression	40 healthy volunteers 20 aggressive subjects	Decreased • HDL-C : total cholesterol ratio • HDL-C • LDL-C : HDL-C ratio	Troisi and D'Argenio [2006]
Physical aggression	29 children with disruptive behavior disorders 43 children with OCD	Decreased • 5-HIAA	Kruesi et al. [1992]
Impulsive aggression	10 healthy volunteers 28 personality disorder subjects	Increased • Glutamate	Coccaro et al. [2013]
Impulsive aggression	20 healthy volunteers 40 personality disorder subjects	Increased • 5-HIAA Decreased • HVA	Coccaro and Lee [2010]
Premeditated aggression	18 males with substance dependence	Increased • Total cholesterol	Conklin and Stanford [2008]
Reactive aggression	158 girls with psychiatric problems	Decreased • Cortisol	Stoppelbein et al. [2014]
Reactive aggression	245 adolescents at risk for psychopathy	Decreased • Cortisol	Poustka et al. [2010]
Reactive aggression	194 boys from longitudinal population study	Increased • Cortisol	van Bokhoven et al. [2005]
Reactive aggression	40 boys at risk for CD	Increased • Cortisol	Lopez-Duran et al. [2009]
Proactive aggression	158 girls with psychiatric problems	Decreased • Cortisol	Stoppelbein et al. [2014]
Proactive aggression	245 adolescents at risk for psychopathy	Decreased • Cortisol	Poustka et al. [2010]

[a]Abbreviations as mentioned in the population column: OCD, obsessive compulsive disorder; CD, conduduct disorder.
[b]Abbreviations as mentioned in the biomarker(s) column: 5-HIAA, 5-hydroxindoleacetic acid; HVA, homovanillic acid; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

Placidi et al., 2001]. MAO converts MHPG into homovanillic acid (HVA), which is most frequently measured when investigating dopamine function. In apparent contradiction with the theory that hyperactivity of the dopaminergic systems leads to increased aggression, low levels of HVA have been associated with total aggression [Table I; van Goozen et al., 1999; Coccaro and Lee, 2010], ODD [Table II; van Goozen et al., 1999], and impulsive aggression [Table III; Coccaro and Lee, 2010].

The main GABA precursor is alpha-ketoglutarate (α-KG), a tricarboxylic acid (TCA) cycle intermediate. Glutamate dehydroxylation of α-KG synthesizes glutamate, which is then converted into GABA by glutamic acid decarboxylase (GAD) [Soghomonian and Martin, 1998; Bak et al., 2006]. In aggressive animals, low levels of neuronal GABA and GAD have been observed [de Almeida et al., 2005], and inhibition of GABA re-uptake (leading to higher postsynaptic GABA levels) inhibits aggressive behavior [Siever, 2008]. Congruently, low plasma levels of GABA are observed in human individuals with high total aggression scores [Table I; Bjork et al., 2001]. Increased levels of CSF glutamate have been associated with increased total and impulsive aggression in humans [Table I and III; Coccaro et al., 2013]. Neuronal GABA levels are influenced by 5HT (through unknown mechanisms) and positively modulate $GABA_A$ receptor activity which increases alcohol-induced aggressive behavior [de Almeida et al., 2005). In contrast, positive modulation of $GABA_A$ receptors with benzodiazepines decreases violent outbursts in psychiatric patients [de Almeida et al., 2005].

The different neurotransmitter systems work in tight concert with one another and with other systems to initiate or inhibit the complex behavior aggression. For example, impaired synaptic 5HT transport (associated with increased aggression) is potentially explained by reduced lipid micro-viscosity due to low central nervous system cholesterol levels [Engelberg, 1992; Wallner and Machatschke, 2009]. Indeed, low serum cholesterol levels have been associated with CD, APD [Table II; Repo-Tiihonen et al., 2002], and premeditated aggression [Table III; Conklin and Stanford, 2008], and a decreased ratio of serum high density lipoprotein cholesterol (HDL-C) to total serum cholesterol has

been associated with verbal aggression [Table III; Troisi and D'Argenio, 2006]. Similarly, for other lipoproteins, such as HDL-C and LDL-C, low levels have also been associated with both total aggression [Table I; Troisi and D'Argenio, 2006; Sahebzamani et al., 2013] and verbal aggression [Table III; Troisi and D'Argenio, 2006]. All these findings support the hypothesis that the association of low CNS cholesterol/lipoprotein levels with increased aggression is mediated through impaired synaptic 5HT transport. Furthermore, glucose levels could influence GABA synthesis as glycolysis synthesizes pyruvate, a necessary metabolite for TCA cycle initiation [Soghomonian and Martin, 1998]. Indeed, low blood glucose levels have been associated with intra-spousal aggression [Bushman et al., 2014]. Finally, influences of the HPA and HPG axes on the neurotransmitter systems have been observed [Summers and Winberg, 2006], including a trifecta effect in which high testosterone, low cortisol and low serotonin lead to impulsive aggression [Montoya et al., 2012] and the modulating effect of DHEA-S on $GABA_A$ receptors [Crowley and Girdler, 2014].

We arrive at indications for the involvement of inflammation markers (e.g., IL-6 and CRP), neurotransmitters (e.g., 5-HIAA, HVA, glutamate, GABA, MAO, and MHPG), lipoprotein markers (e.g., HDL-C, LDL-C, Apo-AI, and Apo-B), and hormones from several classes, including thyroid hormone markers (e.g., triiodothyronine and thyroxin), and steroid hormone markers (e.g., cortisol, testosterone, DHEA[-S], and ACTH) in aggression. These systems and pathways usually have been studied by focusing on one known compound. It is often not known whether this compound is the best one to represent deviation in the pathway or system. Approaches that evaluate a whole metabolic pathway or system may identify the most informative markers, but we can use the current information to guide the selection of pathways.

METABOLOMICS APPROACHES TO BIOCHEMICAL BIOMARKER DISCOVERY

With the complex and heterogeneous nature of aggression, it is unlikely that a single biochemical biomarker can fully represent the aggression phenotype, whereas the combination of multiple biomarkers may reflect the etiology of psychiatric disorders more comprehensively, and hence provide improved insight in the underlying biological processes [Glenn, 2009; Boksa, 2013]. This is even more evident, when we consider the possibility of multiple subgroups with different pathways of pathology, requiring different biomarkers. Most biomarker studies have focused on the quantification and assessment of only a few biomarkers at a time [Zhao and Lin, 2014]. With the advances in techniques for massively parallel analysis [i.e., "omics"-type analyses, that allow for the acquisition of data for many variables in a single analysis of a single biological sample; Dunn et al., 2011a], it now is possible to aid in diagnosis and subclassification based on a large range of biochemicals [Alawieh et al., 2012; Kobeissy et al., 2013]. One of these "omics" approaches, that is, metabolomics, aims at providing a holistic overview of the metabolome of a biofluid (e.g., blood, saliva, cerebrospinal fluid, urine) or tissue sample [Wishart, 2007]. The metabolome compromises all low molecular weight (<1 kDA) molecules that are involved in metabolic reactions (i.e., metabolites) and that are present in the biofluid or tissue under consideration [Dunn and Ellis, 2005].

In metabolomics, typically, two types of strategies are considered: "targeted" and "untargeted." In targeted analyses, the researcher targets the analysis to a relatively small number of metabolites or a selected metabolic pathway, based on some prior hypothesis of the involvement of these metabolites in the biological process of interest. Untargeted approaches, on the other hand, do not depart from a particular biological hypothesis but attempt to obtain an overview of the metabolites in the metabolome that is as broad ("global") as possible [Dunn et al., 2011b]. The untargeted approach is narrowed somewhat in practice by the selection of the platform for analysis focusing on for instance amines, oxidation products or steroids, and more importantly by the sensitivity of the analytical technology chosen. An overview of a typical metabolomics workflow, regardless of the choice for targeted or untargeted approach, for a biomarker discovery study is depicted in Figure 1. The many considerations that apply to the experimental design and sample collection and storage are beyond the scope of this paper and are not discussed, but we will include an outline of the data

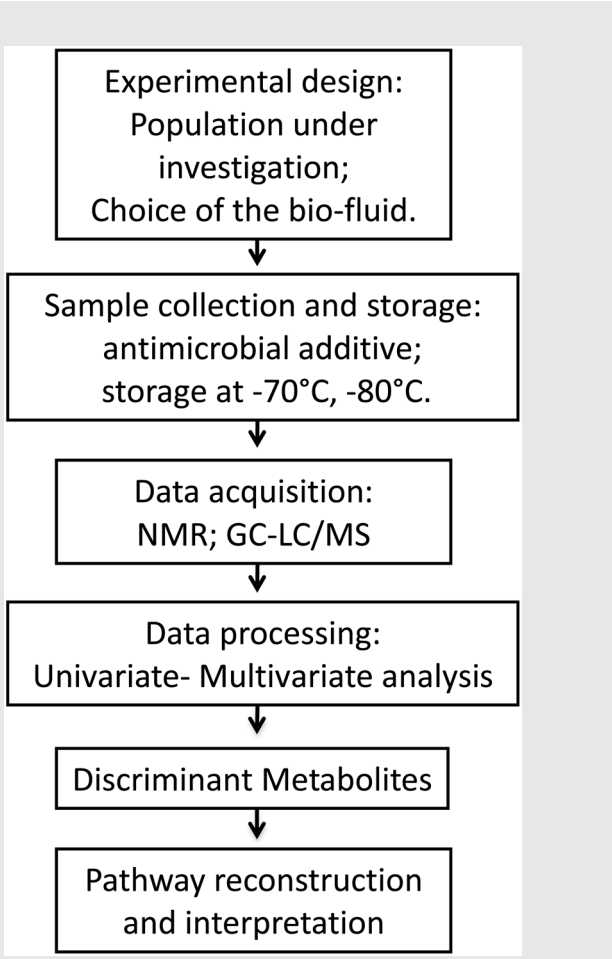

FIG. 1. Aspects of a typical metabolomics biomarker discovery workflow.

acquisition. The two main analytical technologies routinely applied in metabolomics are nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). Both NMR and MS can be preceded by a separation step (leading to so-called "hyphenated" methods), such as liquid chromatography (LC) or capillary electrophoresis. Such separation steps allow for the targeting of the analysis to specific groups of compounds in targeted metabolomics approaches, but hyphenated methods are also being applied in global metabolomics [Patti et al., 2012]. The main difference between NMR and MS is the analytical sensitivity (i.e., the detection limit ranges). The analytical sensitivity of NMR ranges between μM and mM. Therefore, for quantification below μM a more sensitive technique needs to be used. MS sensitivity allows detection of small molecules reaching concentrations in the nM range. NMR and MS have their own relative advantages and disadvantages [Griffin, 2006]. Blow [2008] gave an accessible "technological feature" overview of metabolomics, including a list of commercial metabolomics providers. Many of the commercial options discussed by Blow [2008] are routinely and widely used in modern metabolomics studies. However, additional suppliers (e.g., the Finnish NMR BrainShake platform [http://www.brainshake.fi]) have since been introduced.

In the analysis of metabolomics data, univariate methods fail to differentiate among groups if there is little variance on the single molecule level and the use of multivariate statistical methods is needed to capture not only modification of levels of single metabolites, but also the correlation among the molecules. Such correlations among the molecules are often present, as many metabolites measured on a particular metabolomic platform are biochemically related. A typical problem in the analysis of metabolomics data is the so-called "small *N*, large *p*" problem (relatively small number of samples, relatively large number of variables.) This may make the application of multivariate statistical approaches such as MANOVA impossible and multivariate techniques tend to include principal component analysis (PCA), an unsupervised method, used to give an overview of the data and to identify clusters, trends and outliers; and supervised methods for pattern recognition such as partial least squares regression, and discriminant analysis. From a supervised analysis the set of VIPs (important variables on the projection [Wold et al., 2001]), the main metabolites responsible for the separation, can be identified [Barker and Rayens, 2003; Trygg et al., 2007]. These VIPs are important for diagnostic development, but not enough to understand mechanisms. One way to overcome this limitation is using tools that correlate VIPs with the chain of reactions of their metabolic pathways. The challenge is to identify proper routes through the metabolic network that connect metabolites from a large number of routes that can exist between two compounds [Feist et al., 2009]. Here the multiple other metabolites tested, showing a change, but not reaching a status of VIP are of importance.

Potential Advantages of Metabolomics for Aggression Research

Metabolomics techniques have the ability for providing increased insight in compounds associating with the traditional biochemical biomarkers and provide the promise of finding better discriminating metabolites for diagnostic purposes. Here, we give some examples. In the context of aggression research, where the results of enzymatic determination suggested a role of HDL-C in verbal aggression in aggressive individuals [Troisi and D'Argenio, 2006], serum NMR metabolomics could provide a more detailed profile of the associated lipoprotein subclasses. The promise of this approach is suggested by a study of associations of metabolite concentrations with leukocyte gene expression. In this study, associations of opposite direction were observed for small and large HDL particles [Inouye et al., 2010]. Metabolomic profiling of different aggression subtypes might enable the identification of metabolic biomarkers that are shared across these subtypes [Loscalzo et al., 2007; Holmes et al., 2008], for example, by meta-analysis of the results of (non-targeted) metabolomics experiments [Patti et al., 2012].

Several ratios of biomarkers have been associated with aggression (e.g., the Apo A-I to Apo B or LDL-C to HDL-C ratios [Troisi and D'Argenio, 2006]). Metabolomics would be particularly suited for further investigation of such ratio's by measuring multiple metabolites and calculating metabolite ratios that are underlying the biomarker ratios. This will provide insight into the molecular/enzymatic turnover between metabolites. The translation of biomarkers to metabolite data adds to mechanistic research. Investigations into the genetic architecture of metabolites report moderate to high heritability estimates for their concentrations [e.g., Draisma et al., 2013, 2015; Shin et al., 2014] and genome-wide association studies have identified numerous loci associated with the concentrations of many metabolites; a significant number of the observed locus-metabolite associations provides insight in the underlying metabolic pathways [Dharuri et al., 2014]. Therefore, we suggest that these metabolite quantitative trait loci identify a set of promising candidate genes for aggression when the concentrations of their associated metabolites have been found to be associated with aggression.

An advantage of metabolomics involves the ability to detect substances derived from environmental exposures such as nutrition, for example tryptophan or essential fatty acids. Such nutrient-derived markers might serve as markers of exposure [Suhaimi and Jalaludin, 2015] to exogenous environmental risk factors. Nutrients directly or indirectly interact with numerous non-exposure biomarkers. Due to the critical role of such nutrient effects several "intervention-type" studies have investigated their role in aggression. For example, a study investigating the potential reduction in child and adolescent antisocial and aggressive behavior with omega-3 supplementation, including the essential fatty acid alpha-linolenic acid (αLA), reported significant declines in self-reported reactive and proactive aggression after omega-3 supplementation [Raine et al., 2014]. Various other studies have reported similar beneficial effects of omega-3 supplementation on aggression in other populations, including young adult men [Long and Benton, 2013] and females with BPD [Zanarini and Frankenburg, 2003], in contrast, other studies reported increased aggression after omega-3 supplementation, including populations of school-aged children [Itomura et al., 2005] and patients with comorbid major depressive disorder and substance use disorder [Beier et al., 2014]. While these kinds of supplement studies identify fatty acid metabolism as a possible mechanism underlying aggressive behavior, metabolomics studies might be able to deter-

mine which of the fatty acids included in the supplements have a positive influence on the reduction of aggressive behavior.

Biomarker Discovery With Metabolomics in Psychiatry

Metabolomics is gaining popularity in the study of psychiatric disorders [Kaddurah-Daouk and Krishnan, 2009]. From February 2004 till November 2015, 58 hits for human "metabolomics" AND "psychiatry" are listed in PubMed. Phenotypes include autism [e.g., West et al., 2014; Wang et al., 2015], bipolar disorder [e.g., Howells et al., 2013; Kurita et al., 2015], addictive disorders [Patkar et al., 2009], major depressive disorder [e.g., Paige et al., 2007; Liu et al., 2015], and schizophrenia [e.g., Liu et al., 2014; Wood and Holderman, 2015]. Two reviews by Sethi and colleagues summarize different "-omics" strategies for biomarker discovery in neuropsychiatric disorders [Sethi and Brietzke, 2015; Sethi et al., 2015]. Here, we focus on examples from adult (schizophrenia) and childhood (autism) psychiatric disorders to illustrate how metabolomics can contribute to the study of (pathological) aggression.

In a metabolomics study of autism, metabolic changes in serum between cases and controls were detected. In a discovery phase of 73 patients and 63 controls, 17 metabolites were identified as potential autism biomarkers. In an independent cohort of 100 cases and 100 controls, 11 of the metabolites were replicated. Multiple logistic regression modeling indicated that sphingosine 1-phosphate and docosahexaenoic acid were potential autism biomarkers [Wang et al., 2015]. Metabolic differences in peripheral blood mononuclear cells from schizophrenia cases and controls were investigated in a training set of 45 patients and 50 controls and 18 metabolites discriminated between cases and controls. Differences in pyroglutamic acid, sorbitol, and tocopherol-α replicated in 24 patients and 35 controls [Liu et al., 2014]. These studies indicate the promise of metabolomics in distinguishing between cases and controls, in both children and adults. This is especially impressive when considering the relatively small samples sizes, as compared with for example genome-wide association studies, which have proven to be far less successful for many psychiatric disorders.

Our literature survey and those by Sethi and colleagues [Sethi et al., 2015; Sethi and Brietzke, 2015] did not identify applications of metabolomics aggression in humans. However, we might learn from studies in other species since in general metabolite profiles are highly similar between species [van der Greef et al., 2006]. A study of honey bees used exposure to isopentyl acetate, which is the active compound in the honey bee "alarm pheromone" to induce aggressive behavior. The aqueous metabolites were extracted from the honey bee brains at 5 or 60 min after exposure. Targeted metabolomics detected 122 metabolites. Honey bees showed an increase in glucose, fructose, and alanine levels after induced aggression and increased aggression was associated with increased glycolysis and decreased oxidative phosphorylation in the brain, that is, aerobic glycolysis (increased glycolysis relative to oxidative phosphorylation despite adequate availability of oxygen; Warburg effect). Neurotransmitter levels were altered with decreases in GABA, taurine, alpha-ketoglutarate, and increases in glutamate and glycine. Also, oxidative stress was observed in aggressive bees, with an increase in nitrotyrosine and a decrease in taurine and glutathione. This study by Chandrasekaran et al. so far is the only metabolomics study of aggression in model organisms, and points to pathways previously observed in human aggression via "classic" techniques (Tables I–III).

DISCUSSION

Our review included studies with heterogeneous definitions of aggression, varying sample sizes, and heterogeneous methods and biomarkers are considered. Such diversity across studies limited the conclusions. However, based on examples from autism and schizophrenia metabolomics research, well-identified subgroups for training and validation purposes of around 50–100 cases can provide new leads into biomarkers for psychiatric disorders. The validation of new biomarkers needs to be demonstrated with strong consistent associations between the new marker and the condition of interest, and should include high sensitivity and specificity [Xia et al., 2013]. In the case of aggression, the definition of subgroups requires more attention and this approach may have an iterative character, also defining subgroups definitions based on outcomes of biomarker studies. Our review did not include studies and results in which non-significant associations of biomarker levels with aggression were found. This is a limitation that reduces the possibility to exclude biomarkers a priori, however, when implementing untargeted metabolomics one is not dependent on such a priori assumptions. By collecting the data from multiple studies across several biochemical pathways, we have presented an overview of several biochemical biomarkers in aggression. This provides a basis for several platforms of targeted metabolomics for more in-depth analyses of the exact metabolites involved in each system. This would lead to improved diagnostic approaches, hopefully for well-distinguishable subgroups. Using the observed relation between metabolites and genetic loci, this translation of biochemical biomarkers into metabolites provides a possibility to identify mechanisms and target genes. This can be the basis for leaving a "one fits all" treatment heading to individualized treatment and development of medication for aggression.

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REFERENCES

Alawieh A, Zaraket FA, Li J-L, Mondello S, Nokkari A, Razafsha M, Fadlallah B, Boustany R-M, Kobeissy FH. 2012. Systems biology, bioinformatics, and biomarkers in neuropsychiatry. Front Neurosci 6:187.

American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders, 4th edition. Washington, DC.

Archer J. 1991. The influence of testosterone on human aggression. Br J Psychol 82:1–28.

Archer J, Graham-Kevan N, Davies M. 2005. Testosterone and aggression: A reanalysis of Book, Starzyk, and Quinsey's (2001) study. Aggress Violent Behav 10:241–261.

Atkinson AJ, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, Oates JA, Peck CC, Schooley RT, Spilker BA, Woodcock J, Zeger SL, Colburn WA. 2001. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 96:89–95.

Bak LK, Schousboe A, Waagepetersen HS. 2006. The glutamate/GABA-glutamine cycle: Aspects of transport, neurotransmitter homeostasis and ammonia transfer. J Neurochem 98:641–653.

Barker M, Rayens W. 2003. Partial least squares for discrimination. J Chemom 17:166–173.

Barzman DH, Mossman D, Appel K, Blom TJ, Strawn JR, Ekhator NN, Patel B, DelBello MP, Sorter M, Klein D, Geracioti TD. 2013. The association between salivary hormone levels and children's inpatient aggression: A pilot study. Psychiatr Q 84:475–484.

Barzman DH, Patel A, Sonnier L, Strawn JR. 2010. Neuroendocrine aspects of pediatric aggression: Can hormone measures be clinically useful? Neuropsychiatr Dis Treat 6:691–697.

Beier AM, Lauritzen L, Galfalvy HC, Cooper TB, Oquendo MA, Grunebaum MF, Mann JJ, Sublette ME. 2014. Low plasma eicosapentaenoic acid levels are associated with elevated trait aggression and impulsivity in major depressive disorder with a history of comorbid substance use disorder. J Psychiatr Res 57:133–140.

Bjork JM, Moeller FG, Kramer GL, Kram M, Suris A, Rush AJ, Petty F. 2001. Plasma GABA levels correlate with aggressiveness in relatives of patients with unipolar depressive disorder. Psychiatry Res 101:131–136.

Blow N. 2008. Biochemistry's new look. Nature 455:697–700.

Bo S, Abu-Akel A, Kongerslev M, Haahr UH, Bateman A. 2014. Mentalizing mediates the relationship between psychopathy and type of aggression in schizophrenia. J Nerv Ment Dis 202:55–63.

Boksa P. 2013. A way forward for research on biomarkers for psychiatric disorders. J Psychiatry Neurosci 38:75–77.

Book AS, Starzyk KB, Quinsey VL. 2001. The relationship between testosterone and aggression: A meta-analysis. Aggress Violent Behav 6:579–599.

Bushman BJ, DeWall CN, Pond RS, Hanus MD. 2014. Low glucose relates to greater aggression in married couples. Proc Natl Acad Sci USA 111:201400619.

Chichinadze K, Chichinadze N, Lazarashvili A. 2011. Hormonal and neurochemical mechanisms of aggression and a new classification of aggressive behavior. Aggress Violent Behav 16:461–471.

Coccaro EF, Kavoussi M, Hauger RL, Cooper TB, Ferris CF. 1998. Cerebrospinal fluid vasopressin levels. Arch Gen Psychiatry 55:3–7.

Coccaro EF. 2006. Association of C-reactive protein elevation with trait aggression and hostility in personality disordered subjects: A pilot study. J Psychiatr Res 40:460–465.

Coccaro EF. 2012. Intermittent explosive disorders as a disorder of impulsive aggression for DSM-5. Am J Psychiatry 169:577–588.

Coccaro EF, Lee R. 2010. Cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid: Reciprocal relationships with impulsive aggression in human subjects. J Neural Transm 117:241–248.

Coccaro EF, Lee R, Coussons-Read M. 2014. Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans. JAMA Psychiatry 71:158–165.

Coccaro EF, Lee R, Owens MJ, Kinkead B, Nemeroff CB. 2012. Cerebrospinal fluid substance P-like immunoreactivity correlates with aggression in personality disordered subjects. Biol Psychiatry 72:238–243.

Coccaro EF, Lee R, Vezina P. 2013. Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects. J Psychiatr Res 47:1247–1253.

Collett BR, Ohan JL, Myers KM. 2003. Ten-year review of rating scales. VI: Scales assessing externalizing behaviors. J Am Acad Child Adolesc Psychiatry 42:1143–1170.

Conklin SM, Stanford MS. 2008. Premeditated aggression is associated with serum cholesterol in abstinent drug and alcohol dependent men. Psychiatry Res 157:283–287.

Crowley SK, Girdler SS. 2014. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: What is the current state of knowledge in humans? Psychopharmacology (Berl) 231:3619–3634.

de Almeida RM, Ferrari PF, Parmigiani S, Miczek KA. 2005. Escalated aggressive behavior: Dopamine, serotonin and GABA. Eur J Pharmacol 526:51–64.

de Deurwaerdère P, Navailles S, Berg KA, Clarke WP, Spampinato U. 2004. Constitutive activity of the serotonin2C receptor inhibits in vivo dopamine release in the rat striatum and nucleus accumbens. J Neurosci 24:3235–3241.

Dharuri H, Demirkan A, van Klinken JB, Mook-Kanamori DO, van Duijn CM, 't Hoen PA, Willems van Dijk K. 2014. Genetics of the human metabolome, what is next? Biochim Biophys Acta 1842:1923–1931.

Dmitrieva TN, Oades RD, Hauffa BP, Eggers C. 2001. Dehydroepiandrosterone sulphate and corticotropin levels are high in young male patients with conduct disorder: Comparisons for growth factors, thyroid and gonadal hormones. Neuropsychobiology 43:134–140.

Draisma HH, Beekman M, Pool R, van Ommen G-J, Adamski J, Prehn C, Vaarhorst AA, de Craen AJ, Willemsen G, Slagboom PE, Boomsma DI. 2013. Familial resemblance for serum metabolite concentrations. Twin Res Hum Genet 16:948–961.

Draisma HHM, Pool R, Kobl M, Jansen R, Petersen A-K, Vaarhorst A a. M, Yet I, Haller T, Demirkan A, Esko T, Zhu G, Böhringer S, Beekman M, van Klinken JB, Römisch-Margl W, Prehn C, Adamski J, de Craen AJM, van Leeuwen EM, Amin N, Dharuri H, Westra H-J, Franke L, de Geus EJC, Hottenga JJ, Willemsen G, Henders AK, Montgomery GW, Nyholt DR, Whitfield JB, Penninx BW, Spector TD, Metspalu A, Eline Slagboom P, van Dijk KW, 't Hoen P a. C, Strauch K, Martin NG, van Ommen G-JB, Illig T, Bell JT, Mangino M, Suhre K, McCarthy MI, Gieger C, Isaacs A, van Duijn CM, Boomsma DI. 2015. Genome-wide association study identifies novel genetic variants contributing to variation in blood metabolite levels. Nat Commun 6:7208.

Dunn WB, Broadhurst D, Begley P, Zelena E, Francis-McIntyre S, Anderson N, Brown M, Knowles JD, Halsall A, Haselden JN, Nicholls AW, Wilson ID, Kell DB, Goodacre R. 2011a. Procedures for large-scale metabolic profiling of serum and plasma using gas chromatography and liquid chromatography coupled to mass spectrometry. Nat Protoc 6:1060–1083.

Dunn WB, Broadhurst DI, Atherton HJ, Goodacre R, Griffin JL. 2011b. Systems level studies of mammalian metabolomes: The roles of mass spectrometry and nuclear magnetic resonance spectroscopy. Chem Soc Rev 40:387–426.

Dunn WB, Ellis DI. 2005. Metabolomics: Current analytical platforms and methodologies. TrAC Trends Anal Chem 24:285–294.

Eisenegger C, Haushofer J, Fehr E. 2011. The role of testosterone in social interaction. Trends Cogn Sci 15:263–271.

Engelberg H. 1992. Low serum cholesterol and suicide. Lancet 339:727–729.

Farmer CA, Aman MG. 2011. Aggressive behavior in a sample of children with autism spectrum disorders. Res Autism Spectr Disord 5:317–323.

Farmer C, Butter E, Mazurek MO, Cowan C, Lainhart J, Cook EH, Dewitt MB, Aman M. 2015. Aggression in children with autism spectrum disorders and a clinic-referred comparison group. Autism 19:281–291.

Feist AM, Herrgård MJ, Thiele I, Reed JL, Palsson BØ. 2009. Reconstruction of biochemical networks in microbial organisms. Nat Rev Microbiol 7:129–143.

Glenn AL. 2009. Neuroendocrine markers of psychopathy. In: Ritsner MS, editor. The handbook of neuropsychiatric biomarkers, endophenotypes and genes. Volume 3: Metabolic and peripheral biomarkers. New York, NY: Springer New York. pp 59–71.

Gordis EB, Granger DA, Susman EJ, Trickett PK. 2006. Asymmetry between salivary cortisol and alpha-amylase reactivity to stress: Relation to aggressive behavior in adolescents. Psychoneuroendocrinology 31:976–987.

Griffin JL. 2006. The Cinderella story of metabolic profiling: Does metabolomics get to go to the functional genomics ball? Philos Trans R Soc Lond B Biol Sci 361:147–161.

Haller J. 2013. The neurobiology of abnormal manifestations of aggression—A review of hypothalamic mechanisms in cats, rodents, and humans. Brain Res Bull 93:97–109.

Haller J. 2014a. Hormonal determinants. In: Haller J, editor. Neurobiological bases of abnormal aggression and violent behavior. Vienna, Austria: Springer. pp 33–68.

Haller J. 2014b. Normal and abnormal aggression: Definitions and operational approaches. In: Haller J, editor. Neurobiological bases of abnormal aggression and violent behavior. Vienna, Austria: Spinger. pp 2–32.

Haller J. 2014c. The glucocorticoid/aggression relationship in animals and humans: An analysis sensitive to behavioral characteristics, glucocorticoid secretion patterns, and neural mechanism. In: Miczek K, Meyer-Lindenberg A, editors. Neuroscience of aggression. Berlin, Heidelberg: Springer Berlin Heidelberg. pp 73–110.

Hamon M, Blier P. 2013. Monoamine neurocircuitry in depression and strategies for new treatments. Prog Neuropsychopharmacol Biol Psychiatry 45:54–63.

Hare RD, Hart SD, Harpur TJ. 1991. Psychopathy and the DSM-IV criteria for antisocial personality disorder. J Abnorm Psychol 100:391–398.

Holmes E, Wilson ID, Nicholson JK. 2008. Metabolic phenotyping in health and disease. Cell 134:714–717.

Holtmann M, Poustka L, Zepf FD, Banaschewski T, Priller J, Bölte S, Legenbauer T. 2013. Severe affective and behavioral dysregulation in youths is associated with a proinflammatory state. Z Kinder Jugendpsychiatr Psychother 41:393–399.

Horn M, Potvin S, Allaire J, Côté G, Gobbi G, Benkirane K, Vachon J, Dumais A. 2014. Male inmate profiles and their biological correlates. Can J Psychiatry 59:441–449.

Howells FM, Ives-Deliperi VL, Horn NR, Stein DJ. 2013. Increased thalamic phospholipid concentration evident in bipolar I disorder. Prog Neuropsychopharmacol Biol Psychiatry 41:1–5.

Inouye M, Kettunen J, Soininen P, Silander K, Ripatti S, Kumpula LS, Hämäläinen E, Jousilahti P, Kangas AJ, Männistö S, Savolainen MJ, Jula A, Leiviskä J, Palotie A, Salomaa V, Perola M, Ala-Korpela M, Peltonen L. 2010. Metabonomic, transcriptomic, and genomic variation of a population cohort. Mol Syst Biol 6:441.

Itomura M, Hamazaki K, Sawazaki S, Kobayashi M, Terasawa K, Watanabe S, Hamazaki T. 2005. The effect of fish oil on physical aggression in schoolchildren—A randomized, double-blind, placebo-controlled trial. J Nutr Biochem 16:163–171.

James SJ, Melnyk S, Jernigan S, Cleves MA, Halsted CH, Wong DH, Cutler P, Bock K, Boris M, Bradstreet JJ, Baker SM, Gaylor DW. 2006. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet Part B Neuropsychiatr Genet 141B:947–956.

Kaddurah-Daouk R, Krishnan KR. 2009. Metabolomics: A global biochemical approach to the study of central nervous system diseases. Neuropsychopharmacology 34:173–186.

Kell D. 2004. Metabolomics and systems biology: Making sense of the soup. Curr Opin Microbiol 7:296–307.

Kobeissy F, Alawieh A, Mondello S, Boustany R-M, Gold MS. 2013. Biomarkers in psychiatry: How close are we? Front Psychiatry 3:114.

Kruesi MJ, Hibbs ED, Zahn TP, Keysor CS, Hamburger SD, Bartko JJ, Rapoport JL. 1992. A 2-year prospective follow-up study of children and adolescents with disruptive behavior disorders. Prediction by cerebrospinal fluid 5-hydroxyindoleacetic acid, homovanillic acid, and autonomic measures? Arch Gen Psychiatry 49:429–435.

Kruesi MJ, Rapoport JL, Hamburger S, Hibbs E, Potter WZ, Lenane M, Brown GL. 1990. Cerebrospinal fluid monoamine metabolites, aggression, and impulsivity in disruptive behavior disorders of children and adolescents. Arch Gen Psychiatry 47:419–426.

Kurita M, Nishino S, Numata Y, Okubo Y, Sato T. 2015. The noradrenaline metabolite MHPG is a candidate biomarker between the depressive, remission, and manic states in bipolar disorder I: Two long-term naturalistic case reports. Neuropsychiatr Dis Treat 11:353–358.

Liu M-L, Zheng P, Liu Z, Xu Y, Mu J, Guo J, Huang T, Meng H-Q, Xie P. 2014. GC-MS based metabolomics identification of possible novel biomarkers for schizophrenia in peripheral blood mononuclear cells. Mol Biosyst 10:2398.

Liu X, Zheng P, Zhao X, Zhang Y, Hu C, Li J, Zhao J, Zhou J, Xie P, Xu G. 2015. Discovery and validation of plasma biomarkers for major depressive disorder classification based on liquid chromatography-mass spectrometry. J Proteome Res 14:2322–2330.

Loeber R, Burke JD, Lahey BB, Winters A, Zera M. 2000. Oppositional defiant and conduct disorder: A review of the past 10 years, part I. J Am Acad Child Adolesc Psychiatry 39:1468–1484.

Long S, Benton D. 2013. A double-blind trial of the effect of docosahexaenoic acid and vitamin and mineral supplementation on aggression, impulsivity, and stress. Hum Psychopharmacol 28:238–247.

Lopez-Duran NL, Olson SL, Hajal NJ, Felt BT, Vazquez DM. 2009. Hypothalamic pituitary adrenal axis functioning in reactive and proactive aggression in children. J Abnorm Child Psycho 37:169–182.

Loscalzo J, Kohane I, Barabasi A-L. 2007. Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. Mol Syst Biol 3:124.

McBurnett K, Lahey BB, Rathouz PJ, Loeber R. 2014. Low salivary cortisol and persistent aggression in boys referred for disruptive behavior. Arch Gen Psychiatry 57:38–43.

McEllistrem JE. 2004. Affective and predatory violence: A bimodal classification system of human aggression and violence. Aggress Violent Behav 10:1–30.

Montoya ER, Terburg D, Bos PA, van Honk J. 2012. Testosterone, cortisol, and serotonin as key regulators of social aggression: A review and theoretical perspective. Motiv Emot 36:65–73.

Morrison TR, Melloni RH Jr. 2014. The role of serotonin, vasopressin, and serotonin/vasopressin interactions in aggressive behavior. In: Miczek K, Meyer-Lindenberg A, editors. Neuroscience of aggression. Berlin, Heidelberg: Springer Berlin Heidelberg. pp 189–228.

Narvaes R, Almeida R. 2014. Aggressive behavior and three neurotransmitters: Dopamine, GABA, and serotonin—A review of the last 10 years. Psychol Neurosci 7:601–607.

Nater UM, Rohleder N, Gaab J, Berger S, Jud A, Kirschbaum C, Ehlert U. 2005. Human salivary alpha-amylase reactivity in a psychosocial stress paradigm. Int J Psychophysiol 55:333–342.

Oosterlaan J, Geurts HM, Knol DL, Sergeant JA. 2005. Low basal salivary cortisol is associated with teacher-reported symptoms of conduct disorder. Psychiatry Res 134:1–10.

Paige LA, Mitchell MW, Krishnan RR, Kaddurah-Daouk R, Steffens DC. 2007. A preliminary metabolomic anaysis of older adults with and without depression. Int J Geriatr Psychiatry 22:418–423.

Pajer K, Gardner W, Rubin RT, Perel J, Neal S. 2001. Decreased cortisol levels in adolescent girls with conduct disorder. Arch Gen Psychiatry 58:297–302.

Pajer K, Tabbah R, Gardner W, Rubin RT, Czambel RK, Wang Y. 2006. Adrenal androgen and gonadal hormone levels in adolescent girls with conduct disorder. Psychoneuroendocrinology 31:1245–1256.

Patkar AA, Rozen S, Mannelli P, Matson W, Pae C-U, Krishnan KR, Kaddurah-Daouk R. 2009. Alterations in tryptophan and purine metabolism in cocaine addiction: A metabolomic study. Psychopharmacology (Berl) 206:479–489.

Patti GJ, Yanes O, Siuzdak G. 2012. Innovation: Metabolomics: The apogee of the omics trilogy. Nat Rev Mol Cell Biol 13:263–269.

Placidi GP, Oquendo MA, Malone KM, Huang Y, Ellis SP, Mann JJ. 2001. Relationship to cerebrospinal fluid monoamine metabolite levels. Biol Psychiatry 50:783–791.

Platje E, Jansen LM, Raine A, Branje SJ, Doreleijers TA, de Vries-Bouw M, Popma A, van Lier PA, Koot HM, Meeus WH, Vermeiren RR. 2013. Longitudinal associations in adolescence between cortisol and persistent aggressive or rule-breaking behavior. Biol Psychol 93:132–137.

Platje E, Vermeiren RR, Raine A, Doreleijers TA, Keijsers LG, Branje SJ, Popma A, Van Lier PA, Koot HM, Meeus WH, Jansen LM. 2013. A longitudinal biosocial study of cortisol and peer influence on the development of adolescent antisocial behavior. Psychoneuroendocrinology 38:2770–2779.

Poustka L, Maras A, Hohm E, Fellinger J, Holtmann M, Banaschewski T, Lewicka S, Schmidt MH, Esser G, Laucht M. 2010. Negative association between plasma cortisol levels and aggression in a high-risk community sample of adolescents. J Neural Transm 117:621–627.

Raine A, Portnoy J, Liu J, Mahoomed T, Hibbeln JR. 2014. Reduction in behavior problems with omega-3 supplementation in children aged 8–16 years: A randomized, double-blind, placebo-controlled, stratified, parallel-group trial. J Child Psychol Psychiatry 56(5):509–520.

Ramírez JM. 2009. Some dychotomous classifications of aggression according to its function. Organ Transform Soc Chang 6:85–101.

Ramírez JM. 2011. The usefulness of distinguishing types of aggression by function. Int Soc Sci J 61:263–272.

Ramírez JM, Andreu JM. 2003. Aggression's typologies. Int Rev Soc Psychol 16:125–141.

Ramírez JM, Andreu JM. 2006. Aggression, and some related psychological constructs (anger, hostility, and impulsivity). Some comments from a research project. Neurosci Biobehav Rev 30:276–291.

Repo-Tiihonen E, Halonen P, Tiihonen J, Virkkunen M. 2002. Total serum cholesterol level, violent criminal offences, suicidal behavior, mortality and the appearance of conduct disorder in Finnish male criminal offenders with antisocial personality disorder. Eur Arch Psychiatry Clin Neurosci 252:8–11.

Sahebzamani FM, D'Aoust RF, Friedrich D, Aiyer AN, Reis SE, Kip KE. 2013. Relationship among low cholesterol levels, depressive symptoms, aggression, hostility, and cynicism. J Clin Lipidol 7:208–216.

Sari Y. 2004. Serotonin 1B receptors: From protein to physiological function and behavior. Neurosci Biobehav Rev 28:565–582.

Scoriels L, Salek RM, Goodby E, Grainger D, Dean AM, West JA, Griffin JL, Suckling J, Nathan PJ, Lennox BR, Murray GK, Bullmore ET, Jones PB. 2015. Behavioural and molecular endophenotypes in psychotic disorders reveal heritable abnormalities in glutamatergic neurotransmission. Transl Psychiatry 5:e540.

Scott LN, Stepp SD, Pilkonis PA. 2014. Prospective associations between features of borderline personality disorder, emotional dysregulation, and aggression. Personal Disord 5:278–288.

Seo D, Patrick CJ, Kennealy PJ. 2008. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggress Violent Behav 13:383–395.

Sethi S, Brietzke E. 2015. Omics-based biomarkers: Application of metabolomics in neuropsychiatric disorders. Int J Neuropsychopharmacol 1–13.

Sethi S, Hayashi M, Sussulini A, Tasic L, Brietzke E. 2015. Analytical approaches for lipidomics and its potential applications in neuropsychiatric disorders. World J Biol Psychiatry 1–49.

Shin S-Y, Fauman EB, Petersen A-K, Krumsiek J, Santos R, Huang J, Arnold M, Erte I, Forgetta V, Yang T-P, Walter K, Menni C, Chen L, Vasquez L, Valdes AM, Hyde CL, Wang V, Ziemek D, Roberts P, Xi L, Grundberg E, Waldenberger M, Richards JB, Mohney RP, Milburn MV, John SL, Trimmer J, Theis FJ, Overington JP, Suhre K, Brosnan MJ, Gieger C, Kastenmüller G, Spector TD, Soranzo N. 2014. An atlas of genetic influences on human blood metabolites. Nat Genet 46:543–550.

Siever LJ. 2008. Neurobiology of aggression and violence. Am J Psychiatry 165:429–442.

Simpson K, Hons BS. 2001. The role of testosterone in aggression. McGill J Med 6:32–40.

Soderstrom H, Blennow K, Sjodin A-K, Forsman A. 2003. New evidence for an association between the CSF HVA: 5-HIAA ratio and psychopathic traits. J Neurol Neurosurg Psychiatry 74:918–922.

Soghomonian JJ, Martin DL. 1998. Two isoforms of glutamate decarboxylase: Why? Trends Pharmacol Sci 19:500–505.

Soma KK, Rendon NM, Boonstra R, Albers HE, Demas GE. 2015. DHEA effects on brain and behavior: Insights from comparative studies of aggression. J Steroid Biochem Mol Biol 145C:261–272.

Soma KK, Scotti MA, Newman AE, Charlier TD, Demas GE. 2008. Novel mechanisms for neuroendocrine regulation of aggression. Front Neuroendocrinol 29:476–489.

Stalenheim EG. 2004. Long-term validity of biological markers of psychopathy and criminal recidivism: Follow-up 6–8 years after forensic psychiatric investigation. Psychiatry Res 121:281–291.

Stoppelbein L, Greening L, Luebbe A, Fite P, Becker SP. 2014. The role of cortisol and psychopathic traits in aggression among at-risk girls: Tests of mediating hypotheses. Aggress Behav 40:263–272.

Suhaimi NF, Jalaludin J. 2015. Biomarker as a research tool in linking exposure to air particles and respiratory health. Biomed Res Int 2015:1–10.

Summers CH, Winberg S. 2006. Interactions between the neural regulation of stress and aggression. J Exp Biol 209:4581–4589.

Troisi A, D'Argenio A. 2006. Apolipoprotein A-I/apolipoprotein B ratio and aggression in violent and nonviolent young adult males. J Psychiatr Res 40:466–472.

Trygg J, Holmes E, Lundstedt T. 2007. Chemometrics in metabonomics. J Proteome Res 6:469–479.

Umukoro S, Aladeokin AC, Eduviere AT. 2013. Aggressive behavior: A comprehensive review of its neurochemical mechanisms and management. Aggress Violent Behav 18:195–203.

van Bokhoven I, Van Goozen SH, van Engeland H, Schaal B, Arseneault L, Séguin JR, Nagin DS, Vitaro F, Tremblay RE. 2005. Salivary cortisol and aggression in a population-based longitudinal study of adolescent males. J Neural Transm 112:1083–1096.

van de Wiel NM, van Goozen SH, Matthys W, Snoek H, van Engeland H. 2004. Cortisol and treatment effect in children with disruptive behavior disorders: A preliminary study. J Am Acad Child Adolesc Psychiatry 43:1011–1018.

van der Greef FJ, Adourian A, Muntendam P, McBurney RN. 2006. Lost in translation? Role of metabolomics in solving translational problems in drug discovery and development. Drug Discov Today Technol 3:205–211.

van Goozen SH, Matthys W, Cohen-Kettenis PT, Thijssen JH, van Engeland H. 1998a. Adrenal androgens and aggression in conduct disorder prepubertal boys and normal controls. Biol Psychiatry 43:156–158.

van Goozen SH, Matthys W, Cohen-Kettenis PT, Westenberg H, van Engeland H. 1999. Plasma monoamine metabolites and aggression: Two studies of normal and oppositional defiant disorder children. Eur Neuropsychopharmacol 9:141–147.

van Goozen SH, Matthys W, Cohen-kettenis PT, Wied CG, Wiegant VM, van Engeland H. 1998b. Salivary cortisol and cardiovascular activity during stress in oppositional-defiant disorder boys and normal controls. Biol Psychiatry 43:531–539.

van Goozen SH, van den Ban FE, Matthys W, Cohen-Kettenis PT, Thijssen JH, van Engeland H. 2000. Increased adrenal androgen functioning in children with oppositional defiant disorder: A comparison with psychiatric and normal control. J Am Acad Child Adolesc Psychiatry 39:1446–1451.

Vitaro F, Brendgen M, Barker ED. 2006. Subtypes of aggressive behaviors: A developmental perspective. Int J Behav Dev 30:12–19.

Vitaro F, Gendreau PL, Tremblay RE, Oligny P. 1998. Reactive and proactive aggression differentially predict later conduct problems. J Child Psychol Psychiatry 39:377–385.

Wallner B, Machatschke IH. 2009. The evolution of violence in men: The function of central cholesterol and serotonin. Prog Neuropsychopharmacol Biol Psychiatry 33:391–397.

Wang H, Liang S, Wang M, Gao J, Sun C, Wang J, Xia W, Wu S, Sumner SJ. 2015. Potential serum biomarkers from a metabolomics study of autism. J Psychiatry Neurosci 41(1):1–11.

Weinshenker NJ, Siegel A. 2002. Bimodal classification of aggression: Affective defense and predatory attack. Aggress Violent Behav 7:237–250.

Weiss EM. 2012. Neuroimaging and neurocognitive correlates of aggression and violence in schizophrenia. Scientifica (Cairo) 2012:1–12.

West PR, Amaral DG, Bais P, Smith AM, Egnash LA, Ross ME, Palmer JA, Fontaine BR, Conard KR, Corbett BA, Cezar GG, Donley EL, Burrier RE. 2014. Metabolomics as a tool for discovery of biomarkers of autism spectrum disorder in the blood plasma of children. PLoS ONE 9:e112445.

Willner P. 2015. The neurobiology of aggression: Implications for the pharmacotherapy of aggressive challenging behaviour by people with intellectual disabilities. J Intellect Disabil Res 59:82–92.

Wingfield JC, Moore IT, Goymann W, Wacker DW, Sperry T. 2006. Context and ethology of vertebrate aggression: Implications for the evolution of hormone-behavior interactions. Biology of aggression. New York: Oxford University Press. pp 179–210.

Wishart DS. 2007. Current progress in computational metabolomics. Brief Bioinform 8:279–293.

Wold S, Sjostrom M, Eriksson L. 2001. PLS-regression: A basic tool of chemometrics. Chemom Intell Lab Syst 58:109–130.

Wong DT, Perry KW, Bymaster FP. 2005. The discovery of fluoxetine hydrochloride (prozac). Nat Rev Drug Discov 4:950.

Wood PL, Holderman NR. 2015. Dysfunctional glycosynapses in schizophrenia: Disease and regional specificity. Schizophr Res 166:5–7.

Xia J, Broadhurst DI, Wilson M, Wishart DS. 2013. Translational biomarker discovery in clinical metabolomics: An introductory tutorial. Metabolomics 9:280–299.

Yanowitch R, Coccaro EF. 2011. In: Friedman T, Dunlap JC, Goodwin SF, editors. The neurochemistry of human aggression, 1st edition. Cambridge, Massachusetts, USA: Elsevier Inc. pp 151–169.

Yu YZ, Shi JX. 2009. Relationship between levels of testosterone and cortisol in saliva and aggressive behaviors of adolescents. Biomed Environ Sci 22:44–49.

Zalcman SS, Siegel A. 2006. The neurobiology of aggression and rage: Role of cytokines. Brain Behav Immun 20:507–514.

Zanarini MC, Frankenburg FR. 2003. Omega-3 fatty acid treatment of women with borderline personality disorder: A double-blind, placebo-controlled pilot study. Am J Psychiatry 160:167–169.

Zhao Y-Y, Lin R-C. 2014. UPLC-MS(E) application in disease biomarker discovery: The discoveries in proteomics to metabolomics. Chem Biol Interact 215:7–16.

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