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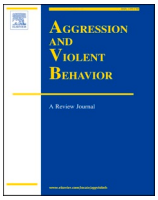

The unusual suspects: A systematic search for the molecular and cellular correlates of human aggression

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ABSTRACT

Decades of research have uncovered several molecules and cell types (i.e., biomolecules) associated with aggression, violence, and hostility (AVH). In this systematic review, we aimed to identify which of these biomolecules have been predominantly studied in relation to AVH in human adults, and to obtain a general sense of the direction of the effects reported for each identified biomolecule. Eighty-one studies (out of 2914 initial abstracts) were included in the review, totaling 198 effects and 29,565 participants. Hormones, particularly testosterone and cortisol, were by far the most studied biomolecules (57.58 %), followed by cytokines (14.14 %), proteins (9.09 %), and neurotransmitters (4.55 %). Out of all extracted statistical effects, 15.1 % reported a negative association, 45.5 % reported no association, and 39.4 % reported a positive association between AVH and the biomolecules, although this pattern varied substantially for individual biomolecules. We also identified some research on biomolecules pertaining to the immune system, which could turn out to play crucial roles in advancing our understanding of AVH. These quantitative insights into the current state of biochemical research on AVH in human adults provide a basis for shaping a broader and more integrative research agenda for studying AVH.

1. Introduction

Aggression is a pervasive phenomenon that disrupts both social and economic stability. Aggression-related incidents generate direct costs in the form of property damage, physical injury, or psychological trauma. It also generates indirect costs since fear of violence influences economic decision-making, primarily by reducing the propensity to invest and consume. The physical and psychological effects of aggression increase the burden on healthcare systems (e.g., due to treating injuries, managing chronic stress-related conditions, and providing mental health services), and can be accompanied by loss of productivity in the workplace (e.g., through direct effects such as absenteeism from injuries or stress and indirect effects such as reduced morale). For instance, one survey reported 741 million productive days lost to sexual, workplace, and/or intimate partner victimization (Peterson et al., 2018). Indeed, the report for Global Peace Index of 2023 estimates that the global economic impact of violence alone was $17.5 trillion in 2022 (12.9 % of the global GDP or $2.200 per capita). Additionally, aggression negatively affects society on several other domains, contributing to lower quality of life, limited access to safe recreational spaces, reduced levels of community and academic engagement, and a general atmosphere of fear and insecurity with an ultimately deleterious effect on mental health (Fowler et al., 2009). The impact of aggression can even transcend generations, as victimized children are at a higher risk of becoming perpetrators themselves (Margolin et al., 2016). Such an economic and societal burden diverts public and private resources, making violence prevention a societal challenge on a global scale.

Terms such as aggression, violence, and hostility (AVH) reflect distinct but related phenomena. Aggression includes all behaviors aimed at harming someone motivated to avoid said harm. Violence refers to

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extreme instances of aggression with the aim of inflicting severe damage or death (Allen & Anderson, 2017). Hostility can be seen as a negative attitude reflecting antagonism and hatred towards others, characterized by distrust, irritability, and high aggression (Gasse et al., 2020; Li et al., 2023). So, these constructs capture different behavioral facets of general aggression. The omnipresence of AVH across species argues in favor of a common evolutionary basis as well as (partially) shared neurobiological mechanisms. A substantial body of research suggests significant modifications in various central nervous system pathways in relation to aggression (Sarkar & Wrangham, 2023), including multiple neurotransmitter systems that seem to play key roles in supporting aggressive behavior (Manchia et al., 2019). Such findings have fueled research on how alterations in such chemical components, as well as their metabolites and precursors, are linked to disbalances supporting the emergence of AVH in humans and animals (Fanning et al., 2020; Sarkar & Wrangham, 2023).

It is believed that animal models can contribute substantially to our understanding of the neurobiology of aggression in humans (Leenaars et al., 2019). At the biomolecular level, a core assumption is that the theoretical translation between animal and human models is possible if a molecule is associated with brain mechanisms that trigger behavioral manifestations of aggression believed to be present across species. A recent primate model based on evolutionary biology (Sarkar & Wrangham, 2023) proposes that there are six biomolecules that are relevant for social functioning (i.e., social signaling molecules), and play central roles in mechanisms underlying human aggression. Briefly, changes in cortisol and testosterone levels have been associated with the presence of social threats and competitors and seem to increase the likelihood of aggression by fostering risk-taking. In contrast, higher serotonin levels have been linked to reduced probability of showing aggression by facilitating cognitive control, behavioral inhibition, and prosocial decision-making (Crockett & Cools, 2015; Siegel & Crockett, 2013). More complex patterns of relationships have been found for oxytocin and vasopressin. These two biomolecules are generally associated with a reduced probability of showing aggression in response to threats. However, oxytocin has been also associated with increased outgroup aggression in many vertebrate species -including humans- and it has thus been proposed to have a context-sensitive “tend and defend” role in social behavior (Triki et al., 2022). A similar picture has emerged for vasopressin, which has been shown to facilitate both defensive aggression (Kawada et al., 2019) and risky cooperation (Brunnlieb et al., 2016) in humans. Note, however, that this hormone has received relatively less attention than oxytocin in the study of human social behavior. Finally, dopamine is considered to be a positive reinforcer for aggression, as aggression appears to trigger dopamine release in the reward circuitry in the brain (Sarkar & Wrangham, 2023). Together, all these molecules exert their influence on the core primate aggression network, which includes brain regions such as the amygdala and the hypothalamus, as well as brain connections that facilitate sensory integration (e.g., thalamus), top-down modulation (e.g., anterior cingulate cortex, orbitofrontal cortex, and medial prefrontal cortex), and motor commands (e.g., periaqueductal gray and supplementary motor area).

The relatively large collection of brain regions involved in aggression implies that it is likely that many more biomolecules have influence in the manifestation of AVH. Indeed, molecules other than the social signaling molecules have been implicated in the expression and regulation of aggression, including estradiol (Nelson & Trainor, 2007), endogenous opioids (Tordjman et al., 2003), and nitric oxide (Chiavegatto et al., 2001). Thus, translational approaches have provided potentially valuable starting points to study the biochemical correlates of aggression in humans, with a particular focus on a select set of neurotransmitters and hormones. However, there is some research pointing towards the involvement of other biomolecules as well. The notion that there should be many more biomolecules involved in AVH seems plausible from at least two angles. The first has to do with the confound introduced by peripheral measures of chemical concentrations. To modulate brain activity, peripheral concentrations of a precursor, neurotransmitter and/or metabolite must cross the Blood Brain Barrier (BBB). There is evidence that the permeability of the BBB is increased in several psychiatric disorders such as schizophrenia, autism spectrum disorders, and affective disorders (Kealy et al., 2020), with also reports of abnormal vascular permeability in violent offenders (Soderstrom et al., 2001). Additionally, several molecules like gliotransmitters, cytokines, glucocorticoids, and histamines are known to produce dynamic changes in the permeability of the BBB (Osipova et al., 2018). This means that these molecules have the potential to moderate the known associations between peripheral concentrations of molecules (e.g., neurotransmitters) and AVH, by regulating the amount of these molecules that effectively cross the BBB and exert their influence on brain activity. Although much less attention has been devoted to these molecules, it is possible that they play a fundamental role in the brain mechanisms subserving AVH.

The second consideration relates to the broader evolutionary perspective applied to the explanation of AVH. Human aggression is an evolved adaptation of patterns of response to environmental circumstances that emerged to foster survival and increase the probability of genetic transmission (Cashdan & Downes, 2012; Sarkar & Wrangham, 2023). As such, multiple brain mechanisms and processes are involved in the manifestation of AVH-like behaviors. It is unlikely that only a handful of molecules are involved in the communication within and between the underlying brain circuits, as well as in other bodily systems (e.g., the gut and the immune system). Prior work has focused on particular mechanisms attached to different bodily systems (e.g., Hypothalamic-Pituitary-Adrenal (HPA) axis, Gut-Brain axis). These studies demonstrated correlations between reduced basal cortisol levels and increased behavioral manifestation of AVH-like behaviors (e.g., Böhnke et al., 2010), and an association between microbiota composition and variability and the manifestation of aggression in both animal models and psychopathological samples (Chen et al., 2021; Gulledge et al., 2023). Notwithstanding the commonly accepted notion that different bodily systems interact to modulate human behavior, no work to date has described how these systems interact in relation to AVH in humans.

In summary, there has been a fair amount of research on the (neuro) biological mechanisms underlying human aggression, but the mechanisms and biological compounds involved are disparate and numerous. This calls for a more structured and integrative view of the current knowledge on the biomolecular correlates of AVH that extends its focus of research beyond the “usual suspects”: testosterone, cortisol, oxytocin, vasopressin, serotonin, and dopamine (Fanning et al., 2020; Sarkar & Wrangham, 2023). There is already evidence pointing towards the importance of other biomolecules. For instance, several studies have investigated whether hostility is linked with gut hormones such as cholesterol (Hillbrand et al., 2000) or leptin (Kienast et al., 2022), whereas others have sought for associations between anger and proteins of the immune system such as interleukins (Koh et al., 2006; Moons & Shields, 2015). The high likelihood that these -and other- molecules play central roles in the explanation of AVH highlights the need for a broader analysis of the existing literature on the biomolecular factors related to AVH. One first step towards broadening the scope of this research agenda is to generate a centralized overview of the biomolecules that have already been studied and the nature of the evidence generated in such studies. Therefore, we conducted a systematic literature search to identify which biomolecules have already been studied in relation to AVH in human adults. A second goal was to generate an overview of the distribution of the statistical effects pertaining to the identified (groups of) biochemical substrates, which provides insights that can help with the assignment of weight to the current evidence when generating claims about the biomolecular correlates of AVH.

2. Methods

2.1. Search strategy

The present review was conducted inaccordance with the PRISMA guidelines (Page et al., 2021) and the PRISMA checklist is available in the supplementary materials section. A systematic search was performed on Pubmed, EBSCOhost and Web of Science using the following search terms included in the title or abstract: (*hostil* OR agress* OR violen* OR antisocial behav* OR anti-social behav* OR violent crim* OR interpersonal crim* OR anger OR angry) AND (chemic* OR protei* OR molecul* OR hormon* OR neurotransmi* OR seroton* OR 5-HT OR cortisol OR alpha-amylase OR GABA OR dopamine OR oxytocin OR vasopressin* OR neuromodula* OR microb* OR bifidobacter* OR lactobacil* OR firmicute* OR bacteroidet* OR gut OR endocrine* OR immune* OR metaboli*) AND (gut* OR *gut OR enteric* OR neurogastro* OR hypothalamic-pituitary-adrenal OR HPA OR stress* OR adrenal OR glucocortic* OR corticotropin OR CRH OR ACTH OR adrenocorticotropic OR pituitary OR hypothalam* OR vagus OR digest* OR gastro*). These terms were optimized to detect any potential associations between AVH and the widest possible range of its molecular and biochemical correlates relatable to bodily systems potentially relevant for the explanation of AVH. The resulting list of publications was uploaded into Rayyan (Ouzzani et al., 2016), and the articles were screened based on the following inclusion criteria:

1. The study sample(s) included only adults that were at least 18 years old.
2. Participants had no documented brain injuries, genetic syndromes, major Axis 1 disorders linked to biochemical disbalances (e.g., psychotic and mood disorders), severe cognitive impairments, physical or medical disorders linked to disturbances at the biomolecular level. These conditions were excluded because it is difficult to untangle whether the biomolecular effects are primarily linked to AVH or to the disease/psychopathology.
3. The study included at least one indication or measure of either aggression, violence, or hostility as an outcome measure.
4. Information about individual molecular and cellular substrates in relation to AVH had to be provided along with corresponding statistical effects.
5. Articles had to be primary quantitative research papers published in peer-reviewed journals.
6. Articles had to be written in English.

Articles were excluded when they:

7. Concerned non-human, animal studies.
8. Included pregnant women, due to the well-known biochemical changes driven by pregnancy.
9. Focused only on victims of aggression, without data on aggression as a main outcome measure.
10. Only reported state measures of anger or negative mood, without a clear link to aggression, violence, or hostility.
11. Included participants that were intoxicated at the time of testing.[1]

2.2. Search results, data extraction, and quality assessment

The search was conducted in June 2023 and identified 5285 records in total (see Fig. 1). An initial screening was conducted to identify duplicate entries and retracted articles. Next, the list of articles was uploaded into Rayan (Ouzzani et al., 2016), and compliance with the inclusion criteria was determined by screening the titles and abstracts and using a two-step approach: two of the authors (TOP and MBR) first examined each of the remaining records independently (*Cohen's kappa* = 0.263, 95 % CI = [0.211, 0.315]) and disagreements arising from the first step (406 articles) were then solved by an independent rater (IAB). The reference lists of the included articles were then hand-searched to identify other relevant studies that were not detected in the initial search. This procedure resulted in the inclusion of 81 independent studies.

Next, data on study characteristics and information pertaining to relevant effect sizes were extracted (see Table S1 in the Supplementary Materials) for each study. The methodological quality of the studies was assessed using an adapted version of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the United States' National Institute of Health (NIH, 2014; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) as in previous systematic reviews (Buric et al., 2017; Dillien et al., 2020). The tool consists of 14 questions (answered with *yes*, *no*, and *not reported/cannot determine/not applicable*) that examine distinct components of the internal validity of the study. We assessed each study on 7 questions adapted from the original tool[2]: (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Was the participation rate of eligible persons at least 50 %? (4) Was a sample size justification, power description, or variance and effect estimates provided? (5) Were the measures (AVH and biomolecules) clearly defined, valid, reliable, and implemented consistently across all study participants? (6) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? (7) When controlling for confounds, were there proper justifications in place?

Finally, we calculated descriptive statistics for all variables of interest, namely sample characteristics (gender, sample type, AVH measure, molecule or cell type, direction of the effects, and study quality).

3. Results

3.1. Description of studies

A total of 81 studies were included in the present review - the PRISMA flow diagram detailing the inclusion / exclusion process is depicted in Fig. 1.

A sum of 29,565 participants were included with an average sample size of 365 participants per study (median = 68 participants, min = 12; max =15,701).[3] From studies where proportions of men and women were reported, 3958 out of 13,724 were women (28.84 %). A total of

[1] Studies including participants with history of substance use were kept in the present review. It is important to consider that substance use has long-term neurological and physiological impacts, which can persist even after termination of use. Nonetheless, considering the highly frequent co-occurrence of substance abuse and antisocial behavior (Koudys et al., 2023; Stetsiv et al., 2023), excluding populations with these comorbidities would be too restrictive.

[2] The original tool was developed to assess both cohort and cross-sectional studies, and items referring to the cohort designs were not applicable to the cross-sectional nature of the studies reviewed here. The following questions were removed from the original tool: "Were all the subjects selected or recruited from the same or similar populations (including the same time period)?"; "For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?"; "Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?"; "For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?"; "Was the exposure(s) assessed more than once over time?"; "Were the outcome assessors blinded to the exposure status of participants?"; "Was loss to follow-up after baseline 20 % or less?"

[3] One study had a sample size of 15,701 participants. When excluded from descriptive statistics, the mean sample size was 173 participants (median = 67.5; max = 4415).

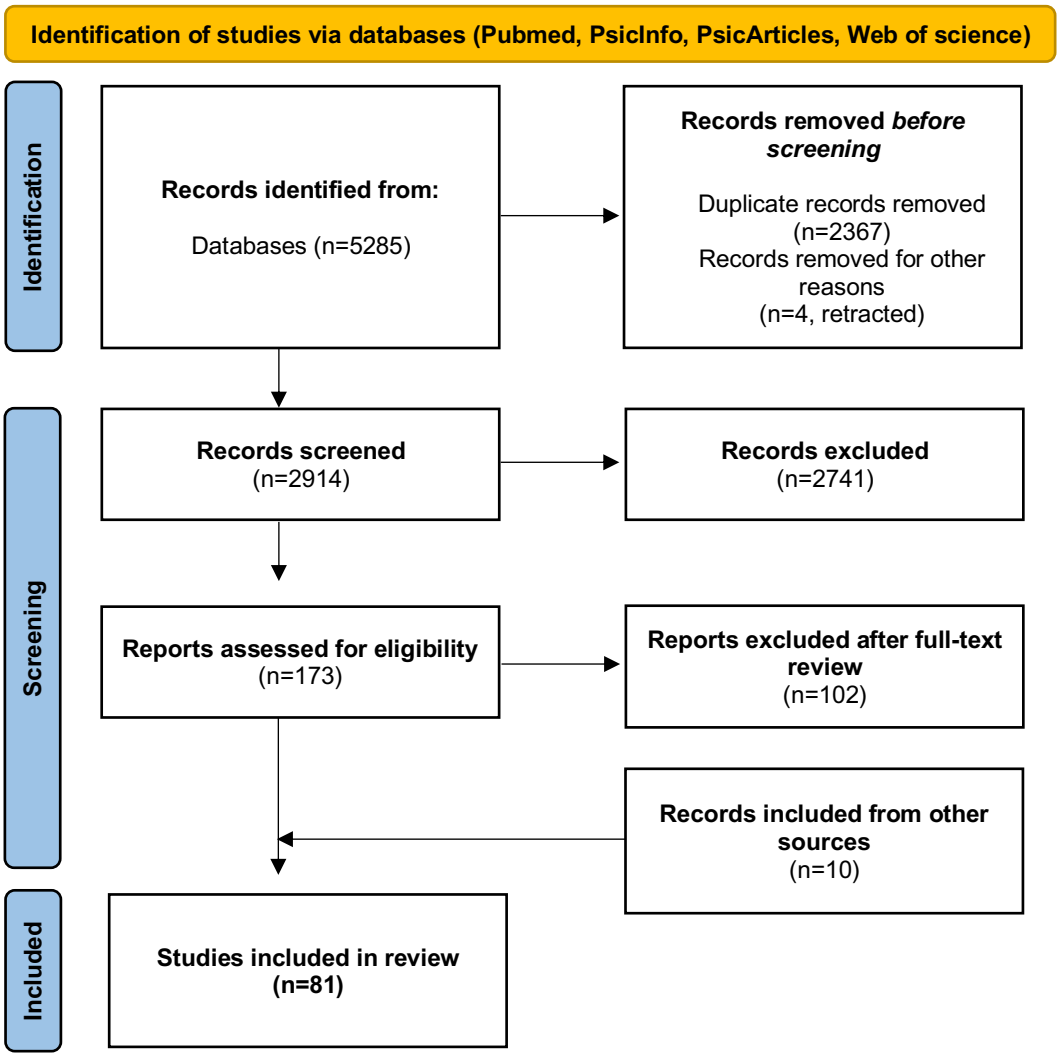


Fig. 1. PRISMA flow diagram mapping the number of records identified, included and excluded, and the reasons for exclusion.

198 effects were retrieved on the relation between molecules and AVH. From those, 177 effects were correlational while 21 consisted in group comparisons (e.g., AVH group vs controls). 132 effects were retrieved from community samples, 34 from samples with history of AVH-like offenses, 23 from patient samples, and 12 from samples with history of substance abuse. Most effects rely on self-reported measures of AVH ($n = 134$), expert ratings of AVH ($n = 19$), and experimental tasks for behavioral assessment of AVH-like behavior ($n = 19$). A summary table of the characteristics of the included studies and effects is depicted in Table S1 (See Supplementary Materials section).

3.2. Synthesis of main findings

Table 1 summarizes the relative frequencies of distinct molecular substrates (based on the number of the reported statistical effects).

57.58 % of the extracted effects concerned tests based on measurements of hormones. Table 2 summarizes the relative amount of extracted statistical effects for different hormones (i.e., the percentage of effects extracted for each identified hormone), showing that cortisol, testosterone, and the Adrenocorticotropic hormone (ACTH) are the most studied hormones.

The overall distribution of the extracted effects shows that 30 effects (15.1 %) reported a negative association, 90 effects (45.5 %) no association, and 78 effects (39.4 %) reported a positive association between AVH and molecules or cells. Fig. 2 depicts the distribution of negative, positive, and no association per ide ntified biomolecule or cell. Fig. 3 depicts the distribution of effects, grouped by molecular or cellular substrate.

Table 1
Percentage of cases with which statistical effects were reported for different types of biomolecules.

Substrate	Frequency
Hormones	57.58 %
Cytokines	14.14 %
Proteins	9.09 %
Neurotransmitter	4.55 %
Antibodies	3.54 %
Lipids	3.03 %
Inflammatory biomarker	2.53 %
Carbohydrates	1.52 %
Other	1.01 %
Lymphocytes	1.01 %
Enzyme	0.51 %
Bacteria	0.51 %
Cytokines	0.51 %
Genes	0.51 %

3.3. Quality assessment of included studies

Each study was assessed by two raters and scores resulted from the

Table 2
Percentage of cases with which statistical effects were reported for different hormones.

Hormone	Frequency
Cortisol	49.12 %
Testosterone	11.40 %
Adrenocorticotropic hormone	10.53 %
Epinephrine	7.02 %
Prolactin	6.14 %
Oxytocin	6.14 %
Growth hormone	3.51 %
Endorphin	0.88 %
Triiodothyronine	0.88 %
Thyroxine	0.88 %
Corticotropin-releasing hormone	0.88 %
Sex hormone-binding globulin	0.88 %
Dehydroepiandrosterone sulfate	0.88 %
Thyroid-stimulating hormone	0.88 %

consensus between the two. Each question was rated with 1 point if the study fulfills the criterion. Of the 81 included studies, 79 fulfilled criterion 1 (clearly stating research question or objective), 76 fulfilled criterion 2 (specification of the study population), 55 fulfilled criterion 3 (participation rate of at least 50 %), 6 fulfilled criterion 4 (sample size justification, power description, or variance and effect estimates), 80 fulfilled criterion 5 (measures clearly defined, valid, reliable), 52 fulfilled criterion 6 (control for covariates and confounds), and 39 fulfilled criterion 7 (proper justification for covariates). The main covariates reported included sociodemographic variables (sex, age), neurobiologically relevant variables (body mass index, blood concentrations of other molecules, metabolism) and controls for AVH measurement (history of previous imprisonment, history of substance abuse). On average, articles have a quality score of 4.77 ($SD = 1.23$; min. = 2; max. = 7). Fig. 4 depicts the absolute frequencies and distribution for each Quality Assessment score.

Importantly, the Quality Assessment scores are identical for the positive, negative, and no association effects: Kruskal-Wallis = 2.76; $p = .252$; $\eta 2 = 0.038$. However, it is possible to observe minimal differences in the distribution of the scores, with negative effects having a higher proportion of slightly lower quality studies (see Fig. 5).

4. Discussion

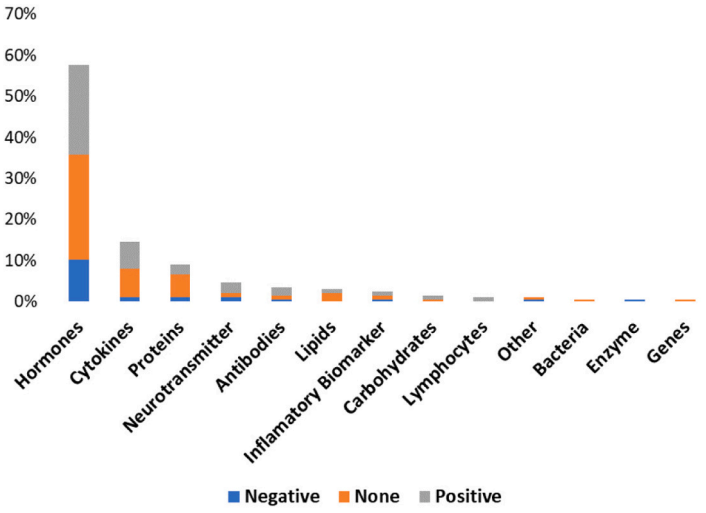
The main goal of the present review was to characterize the extant research on the biochemical correlates of AVH in human adults. Specifically, we sought to quantify which bioactive molecules have been investigated across both experimental and correlational studies on AVH in human adults. Our results highlight that there has been a predominant focus on the involvement of hormones in AVH, particularly on

Molecule	Direction of Effects		
	Negative	None	Positive
Cortisol	6%	12%	11%
Testosterone	-	3%	4%
Adrenocorticotropic hormone	1%	5%	1%
IL-6	1%	3%	2%
NorEpinephrine	1%	1%	3%
C-reactive protein	1%	3%	1%
Epinephrine	-	2%	2%
Prolactin	1%	2%	1%
Oxytocin	2%	1%	2%
TNF-α	-	1%	3%
autoAbs	1%	1%	1%
Growth hormone	1%	1%	1%
Glucose	-	1%	1%
MCP-1	1%	1%	-
IL-18	-	1%	-
IL-8	-	1%	-
IL-10	-	1%	-
Immunoglobulin A	-	-	1%
Composite inflammatory markers	1%	-	1%

Molecule	Direction of Effects		
	Negative	None	Positive
MPO	-	1%	
Tryptophane	-	-	1%
Corticotropin-releasing hormone	-	-	1%
Immunoglobulin G	-	1%	-
Thyroxine	-	1%	-
Dehydroepiandrosterone Sulfate	-	-	1%
CSF-CAA	-	-	1%
16S rRNA Gene	-	1%	-
bleeding time thromboxane B2	-	-	1%
Phytohemagglutinin	-	1%	-
MAOA	1%	-	-
IL-2	-	1%	-
sCD14	1%	-	-
Pro-inflammatory factors	-	-	1%
Leukocyte telomere length	1%	-	-
Anti-inflammatory factors	-	-	1%
Dopamine	-	1%	-
Cell adhesion molecule	-	-	1%
Triiodothyronine	-	-	1%

Molecule	Direction of Effects		
	Negative	None	Positive
Docosahexaenoic acid	-	1%	-
Thyroid-stimulating hormone	-	1%	-
Lymphocytes	-	-	1%
Natural killer cell acitivity	-	-	1%
Endorphin	-	-	1%
LBP	-	-	1%
Toxicity-preventing activity	-	1%	-
IL-1	-	-	1%
Plasma protein	-	1%	-
28RFa	-	1%	-
Microhematocrit	-	1%	-
Triglyceride	-	1%	-
Migration Inhibitory Factor	-	1%	-
Sex hormone-binding globulin	-	-	1%
IL-1β, IL-8, TNF-α, IL-1α	-	-	1%
LDL	-	1%	-
HDL	-	1%	-
Cholesterol	-	-	1%

Fig. 2. Graphical (top) and tabulated (bottom) depictions of the relative distributions of the direction of statistical effects per identified biomolecule.



Types of molecule	Direction of effects		
	Negative	None	Positive
Hormones	10%	26%	22%
Cytokines	1%	7%	7%
Proteins	1%	6%	3%
Neurotransmitter	1%	1%	3%
Antibodies	1%	1%	2%
Lipids	-	2%	1%
Inflamatory Biomarker	1%	1%	1%
Carbohydrates	-	1%	1%
Lymphocytes	-	-	1%
Other	1%	1%	-
Bacteria	-	1%	-
Enzyme	1%	-	-
Genes	-	1%	-

Fig. 3. Graphical (left) and tabulated (right) depictions of the relative distributions of the direction of statistical effects for different types of biomolecules.

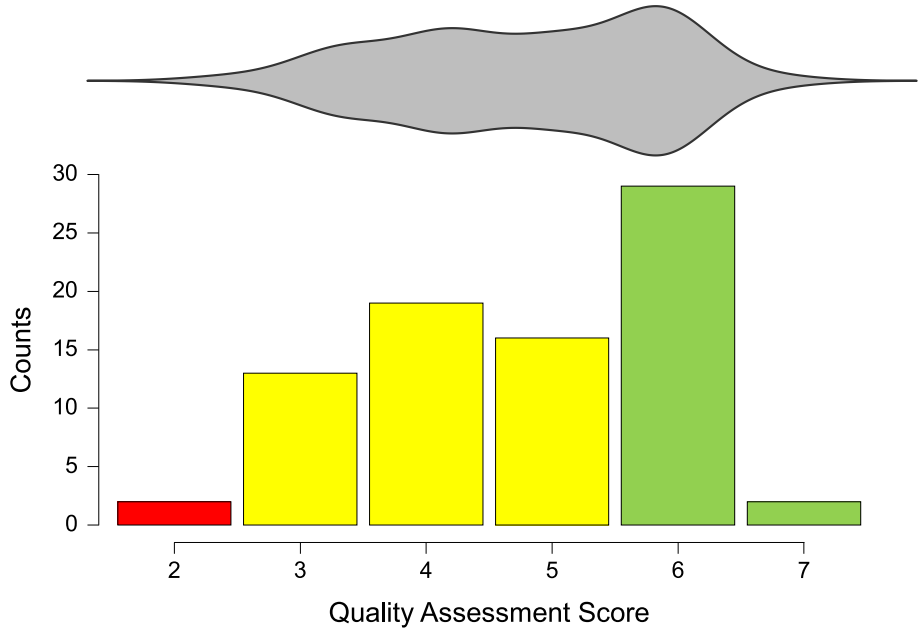


Fig. 4. Distribution of quality assessment scores across studies.

cortisol and testosterone (Dekkers et al., 2019; Figueiredo et al., 2020; Geniole et al., 2020). Strikingly, we also found that other hormones with an established role in non-human animal aggression, such as vasopressin, oxytocin, serotonin, and dopamine (Sarkar & Wrangham, 2023), seem to be generally understudied in human adult studies on AVH. Another relevant finding is that there is a substantial body of work relating AVH to biomolecular agents pertaining to the immune system, although the amount of research on this topic is far less prominent compared to endocrine studies in AVH. We also found that there was no clear trend in the direction of the reported effects, as there were similar distributions of statistical effects across studies reporting positive, negative, and no associations. We also observed that there are very few studies and reported effects for other molecular substrates as well, such as lipids, carbohydrates, or enzymes. We observed that there were no trends in the directions of the reported effects, with comparable frequencies for reports of no association and positive association between AVH and biomolecular measurements.

As noted in the introduction, vasopressin, oxytocin, serotonin, and dopamine have been shown to not only relate with aggression in particular, but also to brain mechanisms with a more general function. Such mechanisms include cognitive control, social bonding, and reinforcement learning, which are in turn involved in AVH (Blair, 2013, 2022; Sarkar & Wrangham, 2023). As such, it is likely these molecules are involved in the complex chain of biomolecular factors that explain AVH. From this perspective, the involvement of the immune system in AVH could turn out to be a missing link in the search for the etiological factors driving AVH. One reason why this seems plausible is that, besides its primary function of protecting the organism against pathogens, the immune system also induces changes in behavior. A recent study using animal models showed that allergen ingestion was associated with a cascade of molecular reactions that induced activation in brain areas such as the nucleus of tractus solitarius and parabrachial nucleus in the brainstem and central amygdala, all known for their involvement in generating responses to aversive stimuli (Florsheim et al., 2023). This

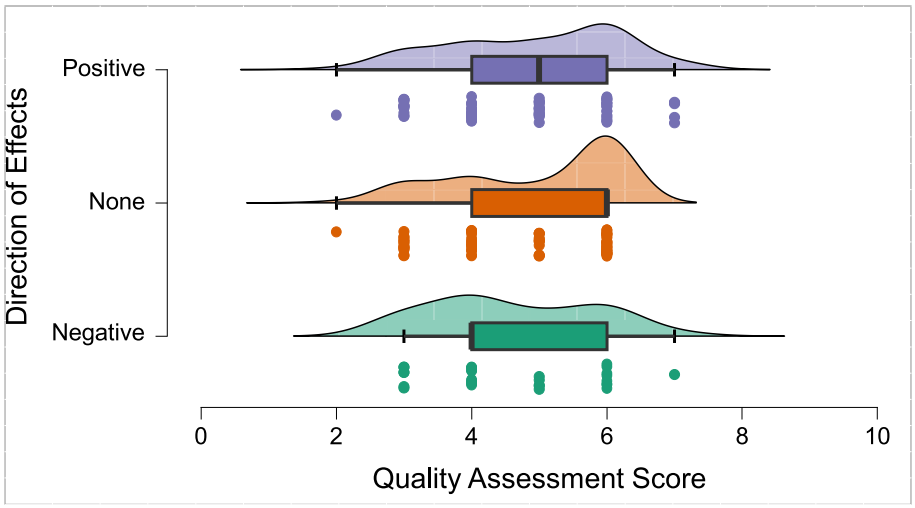


Fig. 5. Distribution of the quality assessment scores across studies, grouped based on the direction of the reported statistical effects for the association between biomolecules and AVH.

study is particularly interesting, as it connects the immune system's response to allergens with avoidance behavior (i.e., not licking contaminated liquids), highlighting the immune system's influence on behavior in general. Additionally, an evolutionary perspective on the behavior-immune system connection suggests that many psychological mechanisms (partly) evolved to neutralize infections, which can be connected to social behaviors (Florsheim et al., 2023). In this view, many forms of AVH can potentially be seen as a collection of social behaviors that evolved to help reduce the chance of being exposed to pathogens. This prediction would particularly concern AVH aimed at avoiding physical confrontations with others that could lead to wounds or other types of injury (e.g., threats, provocations, etc.).

One important consideration is that the immune system is highly reliant on gut function (Round & Mazmanian, 2009), indicating that the digestive system probably plays a key role in the emergence of AVH. It has indeed been found that changes in the population of gut microbes can affect desires, moods, and behaviors. Taking such insights into account is particularly relevant for understanding how the immune system, through its interaction with gut microbiota, can influence AVH (Filiano et al., 2016; Kipnis, 2018). However, our analyses of the publication trends showed that the links between molecules active in the immune system and AVH are relatively understudied in humans.

In sum, we found that most studies on the biomolecular underpinnings of AVH in human adults targeted the hormones cortisol and testosterone, with much less focus on other compounds. Specifically, our results show a tendency for higher concentrations of cortisol and testosterone being positively associated with the manifestation of AVH. Both cortisol and testosterone are correlates of sympathetic activation, thus facilitating behavioral manifestation of AVH (Casto & Edwards, 2016). Nonetheless, the high number of cortisol and testosterone studies highlights both a research bias and a gap in the literature, and questions the assumed involvement of multiple hormones in AVH. Studies on biomolecules other than hormones are much scarcer, but there are some studies on the involvement of the immune system in AVH. This highlights the need for a broader research agenda on the relationship between biomolecules and AVH, with a shift of focus away from cortisol and testosterone and towards the examination of other molecular substrates for understanding AVH. A critical assessment of the wide range of biochemical factors in relationship to AVH, besides offering a more holistic understanding of the phenomenon, has the potential to highlight complex causal hypothetical associations between molecular factors, bodily, and brain systems, further informing future research on the molecular determinants of AVH.

4.1. The way forward: methodological and conceptual considerations for optimizing future studies on AVH

When it comes to methodology, there is a growing recognition of the need to integrate multi-domain data to understand the brain's structure and function, as well as its interactions with all the other bodily systems. It has been proposed that such an approach holds the potential of increasing the robustness of behavioral prediction (Calhoun & Sui, 2016). This integration demands high-quality data and robust reporting practices to ensure the data's validity and reproducibility (Voytek, 2022). Our quality assessment indicated that the quality of the reporting was generally unsatisfactory. The most salient issue was that many studies failed to provide a justification for the sample size or any sort of power analysis. Though some decades ago the custom was to determine the sample size arbitrarily, there is now sufficient evidence to establish the number of participants or observations based on previous studies. We highlight not only the need for a priori sample size calculations, but also that statistical power should be included and weighted when discussing the reported statistical effects. Second, many studies only reported the effects resulting from fitted multivariate models, which strongly hinders comparability across studies and model generalizability (Yarkoni, 2022). We recommend also reporting raw, uncorrected effects (e.g., bivariate Pearson correlations) and, if possible, make data openly available. This facilitates meta-analyses and allows for a more precise effect size quantification across studies.

More generally, nevertheless, it should be kept in mind that the accumulation of data and findings per se might not lead to a better understanding of the underlying processes (Jonas & Kording, 2017). Models that integrate the complex and changing interactions between multiple systems are thus needed (Viding et al., 2023). This is further emphasized by the recent discovery of brain activity patterns correlated with gastric (Mayeli et al., 2023; Rebollo & Tallon-Baudry, 2022) or cardiac rhythms (Valenza et al., 2019), and by studies linking body-brain coupling with psychopathology (Judah et al., 2018). Given the association of AVH with proprioception-related factors such as hunger (Bushman et al., 2014), heat (Kim et al., 2023), or resting heart rate (de Looff et al., 2022), exploring covariation between bodily and neural signals is bound to become a fruitful avenue in the study of AVH.

There also is room for improvement in the conceptual domain. The conceptualization and operationalization of AVH posits challenges that are common to all operationalizations of psychological constructs. AVH represents a collection of hypothetical constructs that are unobservable, and thus need to be inferred from observable indices such as behavior and changes in neurobiological measures. Therefore, it should always be

kept in mind that the same behavior can be interpreted in a myriad of ways, depending on the conceptual embedding of choice (Brazil, 2015; Brazil et al., 2018). Therefore, multiple psychological constructs and theories can be generated based on the exact same observations. The emergence of a new theory or construct is often accompanied by the (re-)development of corresponding methodological tools that are fine-tuned to maximize convergent validity with related constructs. This creates a strong dependency between current and previous tests and constructs and constrains empirical exploration as the development of new research and constructs fail to break free from the initial operationalizations (Moreau & Wiebels, 2022). As a result, a new theory generates optimized instruments that confirm its validity, leading to competition among empirically valid theories that all try to explain the same phenomena but differ in how the corresponding constructs are operationalized and which facets of the target phenomena they capture (Lilienfeld et al., 2016; Miller & Lynam, 2012). One solution could be to take a multi-level approach to theory-building as well by developing integrative frameworks that allow for both level-specific and multi-level research (Brazil et al., 2018; Smeijers et al., 2019; Viding et al., 2023). Such a framework could accommodate research on behavioral AVH as individual levels and would also specify a way to embed them as different levels or facets that can be integrated to provide a better coverage of the underlying latent construct, which in this case could be general aggression. It can be expected that this type of approach would also help create more conceptual clarity, as it forces us to consider how exactly the level-specific constructs included are mutually related, overlap and differ. One example is the use of state anger measurements to capture AVH. During the screening phase of the review process, we observed that several studies equated stable predispositions to show AVH with state anger and/or related negative mood states. Though anger is important due to its impact on cardiac (Smaardijk et al., 2020) and general health (Barefoot & Williams, 2011), among other reasons, we argue that it is better understood as a predisposing factor for AVH, rather than as an outcome per se. This suggestion is in line with research showing that anger may only translate into aggression under certain facilitatory conditions (Kruithof et al., 2024). This example points out why it is important to find new ways to chart the conceptual and mechanistic links between constructs relevant to our understanding of aggression in general. Moreover, it also accentuates the urgent need to define the boundaries within which it is permissible to extrapolate the interpretation of empirical findings.

Based on the studies that reported sex distribution data, women constitute fewer than 29 % of the participants in this review. This discrepancy questions the degree to which findings of the present review—and, by extension, the broader understanding of the biochemical correlates of AVH – can be considered applicable to both men and women populations. The need for generalization boundaries also can be found in the tendency to translate findings on AVH obtained in non-human animals to human beings. The case of testosterone offers a cautionary tale in this regard. This hormone has a positive net impact on human aggression (Geniole et al., 2020), though this association is substantially smaller and less consistent than in animals (George & Rosvall, 2022). Also, research has shown that oxytocin potentiates coalitionary aggression and infant defense in animals (Sarkar & Wrangham, 2023), but it remains unclear whether oxytocin may also have a similar effect in humans. Besides these examples, the results of our literature search clearly indicate that there is a lack of human studies for most of the hormones that have been linked to AVH through animal research. Thus, cross-species generalization requires a careful consideration of the contextual modulators and boundary conditions of the associations (Yarkoni, 2022). This also highlights the importance of generating appropriate theoretical frameworks and working hypotheses, while acknowledging that such frameworks cannot accommodate all possible biomolecular correlates of AVH.

This notion was also implemented in our search strategy to include multiple bodily systems that may modulate the brain mechanisms underlying AVH. One drawback of this approach is that it increases the chance of excluding studies that were not clearly linked to such bodily systems. For example, we found a relatively low number of studies reporting effects on, for example, vasopressin, oxytocin, serotonin, and dopamine. It could be the case that studies on, e.g., dopamine and vasopressin in relation to AVH that were not clearly linked to such systems remained undetected. Another reason could be that we excluded studies on patients with neurological and/or major Axis I disorders, and that such studies in special populations are the ones usually used to study AVH in relation to, for example, serotonin (Duke et al., 2013). Lastly, the inherent difficulty of quantifying neurotransmitters in the central nervous system could have played a role in failing to find studies on these biomolecules. As most neurotransmitters are produced in the brain, there is no clear correspondence between concentrations in cerebrospinal fluid and those in blood or saliva (Audhya et al., 2012; Egri et al., 2020). This stands in contrast to hormones -which are produced in many glands outside of the central nervous system-, or immune cells -most of which are produced in bone marrow-, and that can thus be quantified more easily in peripheral measurements. Despite the possible underrepresentation of studies on the most common neurotransmitters, given the scarcity of studies and theories on most types of biomolecules it seems unlikely that the overall pattern of results would be completely different after inclusion of studies that were potentially missed. Moreover, our approach has the advantage of widening the scope of the link between molecules and aggression, by targeting bodily systems with known connections with the central nervous system.

5. Conclusion and final remarks

Taken together, our review reveals that hormones have been overrepresented in the study of AVH in human adults. Surprisingly, the impact of other potentially important biomolecular correlates of AVH, such as dopamine, norepinephrine, and those related to immune function, is yet to be quantified despite their relatively established influence on aggressive and violent behavior in non-human animals. Moreover, our findings revealed some research on the involvement of the immune system and the digestive system in AVH, but that this line of work in human adults is in an initial stage relative to research on testosterone and cortisol. This incipient subfield is likely to yield important insights in the understanding of AVH, as it may widen the traditional scope of research in the field and contribute to form a more integrative and necessarily nuanced view of the phenomenon. Our results also provided insights into areas that need to be improved in future studies, such as better reporting, methodological limitations that need to be overcome, the importance of further conceptual refinement, and the potential of developing new multi-level frameworks that would allow for both a more detailed and a more integrated view of the mechanisms that drive AVH. Such insights shed light on the many opportunities that can be used to push research on AVH forward and inform potential interventions. Specifically, research on biomolecules like serotonin, dopamine, testosterone, and cortisol has long been translated to clinical and intervention settings on AVH, by informing assessment, and pharmacological and behavioral interventions (Da Cunha-Bang & Knudsen, 2021). The refinement of our understanding of the biomolecules and basic mechanisms underlying AVH has the potential to yield better assessments and improve possible interventions to reduce the manifestation of AVH (Brazil et al., 2018).

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CRediT authorship contribution statement

Tiago O. Paiva: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Macià Buades-Rotger:** Writing – review & editing, Writing – original draft,

Methodology, Investigation, Data curation, Conceptualization. **Arielle Baskin-Sommers:** Writing – review & editing, Investigation, Conceptualization. **Inti A. Brazil:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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