



Review article

Studies into abnormal aggression in humans and rodents: Methodological and translational aspects

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ABSTRACT

Here we review the principles based on which aggression is rendered abnormal in humans and laboratory rodents, and comparatively overview the main methodological approaches based on which this behavior is studied in the two categories of subjects. It appears that the discriminating property of abnormal aggression is rule breaking, which renders aggression dysfunctional from the point of view of the perpetrator. We show that rodent models of abnormal aggression were created by the translation of human conditions into rodent equivalents, and discuss how findings obtained with such models may be “translated back” to human conditions when the mechanisms underlying aggression and its possibilities of treatment are investigated. We suggest that the complementary nature of human and rodent research approaches invite a more intense cross-talk between the two sides of aggression research than the one presently observed.

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1. Introduction

According to the World Health Organization, 21.7 million Disability-Adjusted Life Years (DALYs) were due worldwide to violence in 2004; in this respect, violence (surprisingly listed among diseases) ranked 18th among all diseases. A more recent statistic

shows that the worldwide number of deaths attributed to interpersonal violence was over 500,000 in 2012, which considerably over passed deaths attributed to drug use disorders, and those attributed to all forms of anxiety and depression, schizophrenia and epilepsy taken together (World Health Organization, Global Health Observatory Depository). In Europe, 27,626 deaths were attributed to assault in 2014, which is almost two times larger than the figure for the above-mentioned disorders taken together or drug abuse in general (World Health Organization Regional Office for Europe,

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European Detailed Mortality Database). Evidence suggests that a large share of homicides (almost 75% in some studies) are committed by people with responsibility diminished to a certain extent by mental illness (Anckarsäter et al., 2009; Large et al., 2008; Vinkers et al., 2009; Vinkers et al., 2011). In addition, the odds ratio (OR) for violence is increased in aggression-related psychopathologies e.g. antisocial personality disorder (OR \approx 6–12 depending on the study), borderline personality disorder (OR \approx 3–4), psychopathy (OR \approx 6), conduct disorder (OR \approx 3–10) (Coid et al., 2006; Fulwiler and Ruthazer, 1999; Hodgins et al., 2008; Kudumija Slijepcevic et al., 2014; Walsh et al., 2016; Yu and Geddes, 2012).

The implication of mental health in violence demonstrates that one possible way to address the problem is medical. Although the pharmacologic treatment of aggression-related psychopathologies evolved considerably over the last few decades, their efficacy remains modest which implies that their neural mechanisms are incompletely understood (British Psychological Society, 2010; British Psychological Society, 2013; Coccaro et al., 2009; Hamilton and Armando, 2008; Olvera, 2002; Woolfenden et al., 2011). These considerations indicate that the development of novel treatment strategies is imperative. Here we review findings related to the first step of mechanistic and drug development projects, particularly the choice of study methodologies and models. The reason is dual. Firstly, investigation tools are abundant in aggression research, but these have not been systematically ordered into a common conceptual framework. Secondly, the correspondence of human and animal research approaches is poorly established, for which the translational value of animal studies remains unclear, which might be one of the reasons why findings in animals are often neglected (Blanchard et al., 2003).

2. Theoretical considerations

Aggression is usually defined either behaviorally (phenomenological definitions) or functionally (functional definitions). In phenomenological terms, aggression is a behavior that delivers noxious stimuli to another organism (Buss, 1961) or more explicitly: any behavior directed toward the goal of harm and injury (Baron, 1977; Zillman, 1979). In functional terms, aggression is perceived as a confrontational form of resource competition (Darwin, 1871; Archer, 2009; Lindenfors and Tullberg, 2011; Weiger and Bear, 1988). Resources that are competed for may be of immediate, long term, or trans-generational utility (e.g. food, social status, and the transmission of genes to the next generation, respectively). In summary, aggression consists in the delivery of harm with the goal of taking advantage when resources are limited and the delivery of harm is more efficient than negotiation (Haller, 2014). This form of resource competition is ubiquitous: it is employed by all species that are endowed with the capacity of performing it (Evans, 1973; Kravitz and Huber, 2003; van Staaden et al., 2011).

The ubiquitous presence of aggression in the animal kingdom precludes this behavior being abnormal *per se*, for which abnormal aggression in its turn requires a definition of its own. Such definitions, however, are surprisingly scarce in the literature despite the widespread use of the term. Phenomenological definitions of aggression *per se* are of little help in the endeavor of defining abnormal aggression, except if species employed behaviors uncharacteristic to them under certain circumstances (e.g. rats would butt with their heads). Such phenomena were not reported so far. Functional definitions are more promising: one can propose aggression being abnormal if it was dysfunctional in legal and/or psychiatric terms (see Section 3.1). For instance, postictal aggression in epilepsy results from the confused state that follows seizures, and has no particular goal. As such, this goalless form of violent behavior may be viewed as dysfunctional, consequently abnormal. In

intermittent explosive disorder, violent outbursts may have an immediate goal (e.g. responding to a perceived threat) but threats are often wrongly perceived, responses are always out of proportion, and outbursts lower rather than increase social status; in addition, they often result in arrests and court sentences. Therefore, aggression not only lost its function in intermittent explosive disorder (and similar) but it is detrimental to the perpetrator. In the same vein even the clearly gain oriented and often well planned violence of antisocial people is detrimental in the long run, despite some shorter or longer lasting successes in terms of wealth and status. Besides leading to imprisonment, antisocial behavior diminishes life expectancy (Black et al., 1996; Martin et al., 1985; Rydelius, 1988). Moreover, antisocial traits are transmitted to the next generation where recurrent suicide attempts are also increased, i.e. the detrimental effects of this behavior have a trans-generational dimension (Gureje et al., 2011; Mattes and Fink, 1987; Vaughn et al., 2015).

Thus, aggression is abnormal when it has no identifiable aim, or when the potential benefits of competition are by far outweighed by highly predictable costs. Briefly, abnormal aggression is dysfunctional aggression.

3. Operational approaches

3.1. Humans

It transpires from the literature that in practical terms, the question of abnormal aggression revolves around two categorical dimensions in humans: law and mental health. No behavioral approach is evident: there appear no clear-cut criteria based on which one particular aggressive act can be considered normal or abnormal. Part of the human literature tacitly considers aggression being abnormal if it is legally punishable. The same behavior (e.g. a blow delivered to the face) is considered normal in the boxing ring and abnormal (at least problem behavior) in a pub. The other part of the human literature considers aggression abnormal if the perpetrator fulfilled the criteria of a mental disorder as depicted in the diagnostic and statistical manuals of mental disorders (DSM I–V) or the international classifications of diseases (ICD 1–10; World Health Organization, 1993). The legal and mental health approaches overlap to such an extent that they are almost interchangeable. This is shown by both the high prevalence of mental disorders in those convicted for violent crime, and by the way in which aggression-related psychopathologies are characterized. For instance all men in a sample of 16 that were sentenced to death in California had posttraumatic stress disorder, severe depression, substance use disorder or psychosis (Freedman and Hemenway, 2000). Five out of the 16 had all four disorders, 7 had three, and 4 had two of them. No one in the sample had only a single diagnosable disorder nor were any of them without a diagnosis. In addition, all but one had either traumatic brain injury or another type of brain impairment; consequently, the sample had on average 5 neurological or psychiatric problems per person, the smallest number of such problems being 3. Noteworthy, psychiatric examination was not exhaustive, and it is highly probable that inmates had other disorders as well (the presence of antisocial personality disorder is almost certain in all cases). Albeit such dramatic examples of the coincidence between criminal behavior and psychopathology are not being published very frequently, the linkage between the two dimensions is generally believed to be very strong. On the other hand, the criteria of aggression-related psychiatric disorders include rule breaking among the symptoms. DSM-5 explicitly includes rule-breaking among the criteria of conduct, oppositional-defiant and antisocial personality disorders and implicitly in the case of others (e.g. borderline personality disorder,

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