CHAPTER SEVEN

Aggression and Intermittent Explosive Disorder: Medical and Lifestyle Correlates

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Frequent outbursts of anger and impulsive aggression are problematic from more than a behavioral point of view. Numerous studies suggest that such behaviors are unhealthy from a physical and medical viewpoint as well. This chapter will review these issues in terms of medical comorbidity, including cardiovascular disease, traumatic brain injury, and the daily consumption of psychoactive substances and general behaviors related to health.

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Cardiovascular Disease

Persistent anger and displays of aggression have long been thought to affect cardiovascular health. Specifically, studies in the late 1950s first made the connection between anger and coronary disease in the context of certain personality types (Friedman & Rosenman, 1959). These investigators studied 83 males with an "intense, sustained drive for achievement and being continually involved in competition and deadlines" (i.e., the "A" personality group) and 83 males who had the opposite characteristics (i.e., the "B" personality group). Those with the "Type A" personality were found to have a sevenfold increased risk of having clinical coronary artery disease compared to those with the "Type B" personality. The group identified "Type A" personality was described as having free-floating hostility, triggered by minor incidents; time urgency and impatience (i.e., "short-fused"); and a competitive drive leading to "stress" and an "achievement-driven" mentality (see Friedman, 1996). A large longitudinal study followed 3154 healthy men (39–59 years of age) for eight and a half years (Rosenman, Brand, Sholtz, & Friedman, 1976) and found that the risk of coronary artery disease was twice as great for those with "Type A," compared with "Type B" personality. Another report, coming after following the same subjects for an additional thirteen and a half years (Ragland & Brand, 1988), however, concluded that while classic risk factors were associated with coronary heart disease (i.e., systolic hypertension, serum cholesterol, smoking, age), the presence of "Type A" personality was not. Later, it became clear that the key behavioral correlate for coronary heart disease was "hostility" (e.g., anger and aggression) as opposed to other features of the "Type A" behavioral pattern (Williams, 2001). This is consistent with data from a large community survey ($n = 20{,}103$ from the Collaborative Psychiatric Epidemiologic Survey: CPES, Alegria, Jackson, Kessler, & Takeuchi, 2003) which reported that the presence of DSM-IV IED is associated with an increased odds ratio of 1.42 (95% CI: 1.01–1.99) for heart disease, 1.31 (95% CI: 1.08–1.59) for hypertension, and 2.10 (95% CI: 1.29–3.14) for stroke compared with those without IED (McCloskey, Kleabir, Berman, Chen, & Coccaro, 2010). Importantly, these data represent the results after accounting for differences in demographic features as well as presence of other behavioral risk factors for these conditions. This is also in line with observations that elevated levels of C-Reactive Protein (CRP), a marker of inflammation, are associated with coronary heart disease (Libby, Ridker, & Hansson, 2009) and that elevated levels of CPR are also associated with hostility (Suarez, 2004), aggression (Coccaro, 2006;

Marsland, Prather, Petersen, Cohen, & Manuck, 2008), and the presence of DSM-5 IED (Coccaro, Lee, & Coussons-Read, 2014). While it is not known if these elevations are causal to aggression in humans, animal studies suggest that inflammatory mediators can directly increase the expression of aggression in animal studies (Zalcman & Seigel, 2006).

Other Medical Conditions Including Pain and Infection

Other Medical Conditions and Pain

In addition to cardiovascular disease, the reanalysis of the CPES data (McCloskey et al., 2010) revealed elevated odds ratios for those with IED, compared to those without IED, for headache [1.64 (95% CI: 1.40–1.91)], neck/back pain [1.39 (95% CI: 1.19–1.62)], ulcer [1.36 (95% CI: 1.09–1.69)], arthritis [1.31 (95% CI: 1.09–1.58)], and chronic pain [1.27 [95% CI: 1.02–1.58)].

It is notable that each of these conditions is characterized by "chronic pain." Despite the relatively common prevalence (and chronic course) of IED, this association has received little attention in the literature even though those with IED are highly likely to get physically injured as a consequence of aggressive behaviors. For example, an investigation of DSM-III diagnoses in patients ($N=283$) presenting to a clinic for "…mixed chronic pain…" (p. 183) found that almost 17% of men received a DMS-III IED diagnosis (Fishbain, Goldberg, Meagher, Steele, & Rosomoff, 1986) which is remarkable given that DSM-III criteria identify a fraction of those who meet DSM-IV or DSM-5 criteria for IED. Curiously, an IED diagnosis in women was relatively rare (less than 2% of 127 women).

Possible mechanisms for an IED-Pain relationship include issues related to elevated levels of inflammatory proteins and that chronic pain could make one more irritable and less tolerant of stressors. In addition, a history of aggression could be associated with physical trauma that could lead to painful injuries or IED-associated alterations in biologic systems that regulate pain could be in play. However, experimental and longitudinal studies that could help identify the mechanisms responsible for the relationship between pain and IED aggression have yet to be conducted.

Diabetes

While the CPES study did not identify IED as a risk factor for diabetes, another very large ($n=54{,}095$) community study in 19 countries (de Jonge et al., 2014) reports an elevated odds ratio for Type II Diabetes for those with DSM-IV IED compared to those without IED [1.6 (95% CI: 1.1–2.1)].

Notably, the elevated odds ratio for IED and diabetes was similar, if not higher, than that for depression and diabetes [1.3 (95% CI: 1.1–1.5)].

Infection

The role of infectious agents in psychiatric disorders has been investigated in the etiology of a variety of behavioral disorders but not so in aggression. This is surprising in that inflammatory cytokines, typically released during infection, directly applied to selected brain areas can increase defensive aggressive responding in mammals (Bhatt & Siegel, 2006; Hassanain, Bhatt, Zalcman, & Siegel, 2005). In addition, treatment of chronic Hepatitis C infection with interferon is associated with an increase in anger (Kraus, Schafer, Faller, Csef, & Scheurlen, 2003; McHuthison, Gordon, & Schiff, 1998). In fact, acute increases of inflammatory cytokines in response to infectious agents, or to endotoxin (which produces a "sickness syndrome" without infection), is associated with irritability and to a sensitization of the amygdala to increase responding to social threat (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012) which increases the risk of an aggressive encounter (Coccaro, Fanning, Keedy, & Lee, 2016; Coccaro, Fitzgerald, Lee, McCloskey, & Phan, 2016). Finally, in vitro studies have shown that leukocytes from human subjects display a direct relationship between levels of aggression proneness and the magnitude of the inflammatory response (Suarez, Lewis, Krishnan, & Young, 2004; Suarez, Lewis, & Kuhn, 2002) which suggests that those with IED may display stronger, though perhaps impaired, responses to infection.

While little is known about bacterial infection we have found that individuals with IED are at risk for latent toxoplasmosis, a parasite that infects many worldwide. In a recent study in over 300 study participants (Coccaro et al., 2016), those with IED were more likely to be seropositive for IgG antibodies to *Toxoplasma gondii* compared with healthy and psychiatric controls; *T. gondii* seropositivity was also associated with higher aggression but not state depression or anxiety scores. Additional studies are needed to determine if there is a rationale to treat the low-grade inflammation, or latent toxoplasmosis, which may be present in individuals with IED. The medical and comorbid psychiatric problems associated with IED highlight the importance of examining antecedents and correlates of IED in order to identify potential mechanisms of prevention and intervention.

Traumatic Brain Injury

There is little question that serious brain injury can be associated with aggression, particularly when the injury compromises brain tissue in regions

and circuits involved in emotional regulation and aggression. Since individuals with IED engage in frequently acts of aggression it is not surprising that those with IED engage in behavior that increases the risk of suffering a head injury in the context of fighting, playing competitive sports, or automobile accidents. That said, mild traumatic brain injury [mTBI; head injury resulting in alteration of consciousness, posttraumatic amnesia, and/or short-lived loss of consciousness (LOC)] is quite prevalent in the United States, with an estimated occurrence of over 1.3 million such injuries in the United States each year (CDC Grand Rounds, 2013). While a substantial number, this figure likely underestimates the problem because many people experiencing generally mild head injury do not seek medical treatment (Voss, Connolly, Schwab, & Scher, 2015). Data regarding aggression in the postconcussive mTBI phase have been reported in a number of studies (e.g., Dyer, Bell, McCann, & Rauch, 2006; Farrer, Frost, & Hedges, 2012, 2013; Rao et al., 2009; Rosellini et al., 2016; Slaughter, Fann, & Ehde, 2003) and suggest that many with mTBI (e.g., 10%–30%) experience lingering physical and behavioral disturbances, including aggression, well beyond the first few weeks after injury. The directional causality between mTBI and aggression remains in question, though several studies suggest that preexisting disturbances of mood, substance abuse or aggressive behavior, are more predictive of future post-TBI aggressive behavior than the presence of an mTBI itself (Elbogen et al., 2012; Gallaway et al., 2012; MacManus et al., 2012; Rosellini et al., 2016; Tateno, Jorge, & Robinson, 2003).

Our own work in this area finds that those with IED are significantly more likely to have a life history of at least one mTBI compared with healthy and psychiatric controls (Mosti & Coccaro, 2018); Fig. 1. When examined dimensionally, we found that while those with history of a single head injury (with or without LOC) had higher aggression scores than those without any history of head injury, individuals with two or more head injuries with LOC had strikingly higher aggression scores than those with only one head injury (with or without LOC). Accordingly, while individuals with one head injury are modestly more aggressive than those without any head injury, individuals with multiple head injuries with LOC display aggression scores three to four times higher than the former group. One limitation in our study was that we did not have data on the timing of head injury in relation to the onset of aggressive behavior. Thus we cannot, unequivocally, say that the head injuries in the individuals in this sample did not cause aggressive behavior. However, it is more likely that the trait of aggression increased the risk of head injury than the reverse because aggressive behavior begins very early in life (see Chapter on Development of Aggression in this volume) and individuals with this temperament are likely to place themselves in

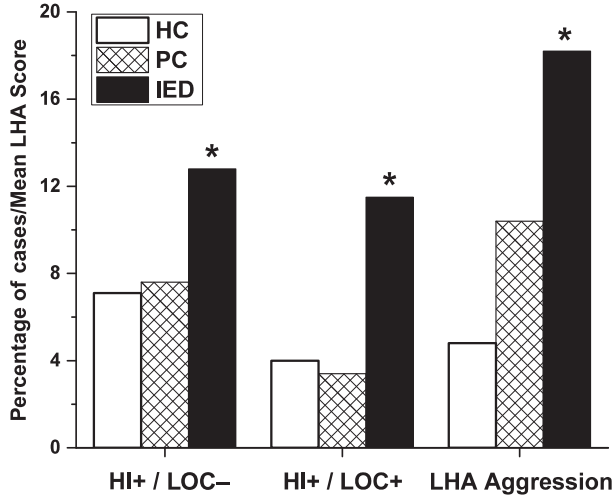

Fig. 1 Percentage of cases with and without history of Head Injury (HI) and/or Loss of Consciousness (LOC) and LHA Aggression Score in healthy (HC) and psychiatric (PC) controls and in those with IED.

circumstances associated with bodily injury. In addition, none of our study participants had head injuries serious enough to result in a loss of consciousness longer than 30 min (mean duration of LOC: 3.7 ± 6.4 min) making these mild, rather than more serious, head injuries in which we would expect grossly long-term altered behavior. Further, these findings are in general agreement with the results of studies examining individuals soon after mTBI which report that premorbid aggression better predicts the occurrence of post-TBI aggression than does recent history of mTBI itself (Dyer et al., 2006; Farrer et al., 2012, 2013; Rao et al., 2009; Rosellini et al., 2016; Slaughter et al., 2003). While more severe TBI can be associated with changes in brain structure and aggression (Epstein et al., 2016), we have found that the lower volumes of fronto-limbic gray matter in study participants with IED were not influenced by history of mTBI (Coccaro, Fanning, et al., 2016; Coccaro, Fitzgerald, et al., 2016). Thus we suggest that the presence of mTBI in these study participants was likely due to the dimensional presence of impulsive-aggressive behavior, across individuals, rather than to a primary effect of mTBI on measures of aggression.

Consumption of "Everyday" Psychotropic Agents

Based on the clear relationship between alcohol and aggression (Parrott & Eckhardt 2018), and on the previous reports of a relationship

between prenatal smoking and antisocial behavior in offspring (Pratt, McGloin, & Fearn, 2006), we have looked more closely at the consumption of "everyday psychotropics" such as alcohol, nicotine (and caffeine) in our reanalysis of the NCS-R study data, our PENN Twins study data, and in our clinical research study participants.

Alcohol

In our reanalysis of the NCS-R data, we found that alcohol use disorder [5.78 (95% CI: 3.79–8.85)] was associated with a higher odds ratio for those with IED, compared to those without IED (Coccaro, Fanning, & Lee, 2017). Specifically, those with IED reported a greater degree of current and lifetime consumption at a trend level of statistical significance compared with healthy, but not psychiatric controls. Dimensional analysis, however, revealed similar relationships between levels of aggression and current ($\beta = 0.10$, $P = .001$) and lifetime ($\beta = 0.10$, $P = .002$) consumption of alcohol.

Nicotine

As with alcohol, we found that nicotine use disorder [4.06 (95% CI: 2.65–6.24)], in the NCS-R reanalysis, was associated with a higher odds ratio for IED, compared to those without IED (Coccaro et al., 2017). Current and lifetime consumption of nicotine was significantly greater among those with IED compared with both psychiatric and healthy controls. In addition, nicotine consumption revealed significant relationships between levels of aggression and current ($\beta = 0.14$, $P < .001$) and lifetime ($\beta = 0.12$, $P < .001$) consumption of nicotine.

Caffeine

While the NCS-R data set did not include information related to the consumption and/or abuse of caffeine, we found, in our clinical research program data set, that current and lifetime caffeine consumption was significantly greater among those with IED and other psychiatric disorders (i.e., psychiatric controls) compared with healthy controls. While levels of caffeine consumption were nonsignificantly higher for IED versus psychiatric control study participants, multiple regression analysis revealed a significant relationship between levels of aggression and current ($\beta = 0.14$, $P < .001$) and lifetime ($\beta = 0.14$, $P < .001$) consumption of caffeine.

Examination of Each Agent Together

When examining the relationship of each of these agents and IED/Aggression, simultaneously, we found that the quantity of current consumption of each correlated directly with levels of aggression for caffeine ($\beta = 0.11$, $P = .001$) and nicotine ($\beta = 0.10$, $P = .002$) consumption, but less so for alcohol ($\beta = 0.05$, $P = .076$). For lifetime consumption, levels of aggression were significantly related to caffeine ($\beta = 0.12$, $P = .001$) and alcohol ($\beta = 0.07$, $P = .049$), but not nicotine ($\beta = 0.05$, $P = .216$), consumption. These data suggest that consumption of these "everyday psychotropics" have a modest, but significant, relationship with aggression across study participants with a wide range of aggression scores.

While detailed neurobiological explanations for these associations are beyond the scope of this chapter, the relationship between aggression and nicotine may relate to observations that cigarette smokers have lower numbers of platelet 5-HT transporters (Patkar et al., 2003). This is quite relevant because lower numbers of platelet (Coccaro, Lee, & Kavoussi, 2009) and brain (Frankle et al., 2005) 5-HT transporters are inversely related with aggression. The relationship between caffeine and aggression, on the other hand, is not fully understood. However, laboratory studies have shown that caffeine administration reduces (Cherek, 1984), while the withdrawal of caffeine (i.e., substituting decaffeinated coffee) increases (Cherek, Bennett, Roache, & Gtrabowski, 1989), aggression in healthy volunteers.

Global Health Issues

Data regarding global health issues were not well represented in the NCS-R study. Thus we have looked at our population-based twin study data to shed light on the possibility of a relationship between general health, exercise, and obesity. These data come from our PENN Twins data set in which we randomly selected one member of a twin pair for examination of a number of behavioral variables (Coccaro & Jacobson, 2006). Since we included a psychiatry screener in that study we also have an estimate of those who self-identify as "angry" to serve as a proxy for IED. Confirming this status, "angry," compared with "nonangry," study participants had substantially higher scores on measures of aggression (BPA Aggression: 38.3 ± 9.8 *vs.* 29.3 ± 8.7, $P < .001$), trait anger (BPA Anger: 23.4 ± 6.0 *vs.* 15.8 ± 5.2, $P < .001$), and impulsiveness (BIS-11 Impulsivity: 71.2 ± 10.4 *vs.* 63.1 ± 9.9, $P < .001$).

General Health

Analysis of our PENN Twins data set reveals that those with self-identified as "angry" are more likely to report poorer general health than those who do not report being "angry" (Fig. 2A).

Exercise

In turn, "angry" study participants were less likely to engage in exercise than "nonangry" study participants (Fig. 2B; unpublished data). Regression analysis confirmed that the higher one's aggression, anger, and impulsivity scores, the less likely individuals engage in regular exercise. When aggression, anger, and impulsivity scores are examined simultaneously, we find that the variance is due to unique influence of trait anger, that is, after trait anger is entered into the statistical model, aggression and impulsivity scores do not add explanatory power to this relationship.

Obesity

Despite rating themselves as in "less" good health (and less likely to engage in regular exercise) as "nonangry" study participants, "angry" study participants did not differ in body mass index (BMI) or differ across BMI-Weight categories (underweight, normal, overweight, obese); Fig. 2C. In addition, aggression, anger, and impulsivity scores did not differ as a function of BMI or "obesity" status.

Summary

Aggression as a dimension and IED as a disorder, in addition to being problematic, may be unhealthy from a physical and medical viewpoint. Hostility has long been associated with cardiovascular problems, and this seems to be true of IED, which carries an increased risk of for hypertension, stroke, and heart disease. IED is also associated with other medical conditions including headaches, arthritis, and chronic pain. These relationships may be in part linked to elevated levels of inflammatory proteins found among individuals with IED. Individuals with IED also show an increased prevalence of mild traumatic brain injury such as concussion, which may be both an antecedent and consequence of aggressive behavior. Finally, those with IED are more likely to use legal drugs such as nicotine and alcohol. Overall, the data strongly supports a relationship between IED and negative health outcomes, though the exact nature of the relationship warrants further study.

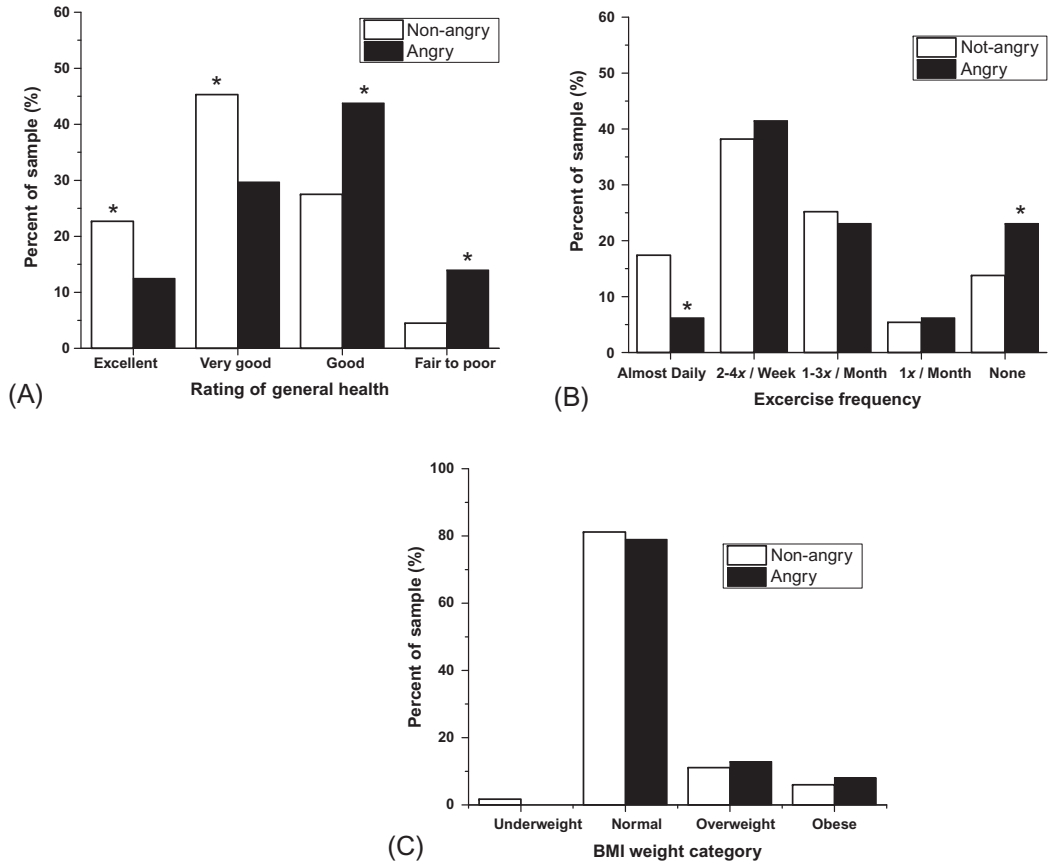

Fig. 2 A. Rating of general health as a function of identifying as having, and not having, "anger issues". B. Rating of exercise frequency as a function of identifying as having, or not having, "anger issues". C. BMI weight category as a function of having, or not having, "anger issues".

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Further Reading

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