CHAPTER SIX

Neuroimaging in Aggression and IED

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Over the past few decades, neuroimaging techniques have been developed to allow observation of both the structure and function of the living brain, shedding light on the neural substrates of behavior, including human aggression. Such work has informed our understanding of brain systems underlying both normal expressions of aggression and the problematic impulsive aggression seen in Intermittent Explosive Disorder (IED). In this chapter, we provide a brief overview of neuroimaging techniques, then highlight and review the contributions neuroimaging studies have made to understanding normal and problematic impulsive aggression.

Overview of Neuroimaging

In research applications of neuroimaging, brain images are acquired through various techniques and then submitted to different measurement and computational procedures, typically yielding quantitative information.

https://doi.org/10.1016/B978-0-12-813858-8.00006-1

This is in contrast to clinical applications of neuroimaging, which usually consist of visual review of images by an expert (e.g., a neuroradiologist) who describes any identified pathology and writes a clinically oriented report. The quantitative information from research neuroimaging goes beyond the qualitative identification of abnormality, as in clinical neuroimaging, and characterizes what are often more subtle relationships between a spectrum of normal to abnormal properties of the brain in relation to diagnosis, behavior, or traits. Neuroimaging clinical populations, such as IED, for research purposes is a heavily multidisciplinary endeavor, involving clinicians, statisticians, bioengineers, physicists, and more.

There are two types of research neuroimaging—structural and functional. Structural imaging characterizes tissues comprising the brain and can be used for volume, shape, or other studies of the brain's physical properties. Computerized tomography (CT) was the first neuroimaging technique, available in the 1970s, providing structural images. CT images allow identification of tissue types (blood, bone, cerebrospinal fluid, or gray and white matter), by the darkness of the grayscale images. Images from CT have played roles in lesion studies linking gross brain alterations to behavioral changes, including in studies relevant to aggression (Herzberg & Fenwick, 1988).

The most prolific neuroimaging technique for understanding human brain–behavior links is, by far, magnetic resonance imaging (MRI). In structural MRI studies, accessible since the 1980s, images can have high enough resolution to allow anatomical measurement at the millimeter scale, with good gray vs. white matter tissue differentiation. Gray and white matter differentiation is important because they serve different functions. Gray matter is mostly neuronal cell bodies. These cells conduct the functions of the brain, such as sensory processing, cognition, and emotional functions, so observations of relatively more or less gray matter, or altered shape of a gray matter structure within the brain, can have implications for how the neurons developed, organized, or are degenerating, and can impact their capacity to fulfill their functions. Studies that utilize cross sectional samples do not typically point directly to any of these interpretations of changes in amount of tissue but can support hypotheses regarding them. However, even longitudinal studies using MRI cannot usually resolve the nature of change at the cellular level. More microscopic methods, animal work, or postmortem tissue analyses are needed. Still, MRI-based observations are important as they document the human brain in vivo and changes can be correlated to behavioral changes,

strengthening conclusions regarding the importance of the brain regions involved, especially in relation to a behavior measured (Johansen-Berg, 2012).

The white matter rendered in conventional MRI is that which comprises white matter tracts, which are cells wrapping around the connecting portions of the gray matter cells (axons of the neurons) reaching across distances to communicate. Thus white matter facilitates connectivity among the brain's subdivided parts, helping form cortico-cortical connections or cortical–subcortical connections. White matter volume can be measured in MRI in a similar fashion to gray matter volume. Relatively less white matter in one group compared to another may indicate poor quality of connections between brain regions, impacting efficiency of communication and function of the connected parts. There is an MRI technique called diffusion tensor imaging (DTI) that is used to study another property of white matter—how freely water is moving within its tracts. As water is generally expected to move within a more restricted longitudinal (oval) shape in accordance with the shape of the white matter cells wrapping around the axons, the metrics from DTI that describe this are taken as observations of the integrity of the white matter. Major white matter tracts traversing larger distances across the brain are easier to render with DTI, and smaller, thinner ones, or places where white matter fibers going different directions intersect, are more challenging to image, but computational approaches combined with more refined MRI acquisitions are improving our capacity to resolve these problems (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010).

Functional neuroimaging renders information about neural activity. Functional MRI (fMRI) is one such technique. First used in research starting in the 1990s, fMRI involves collecting an image of the brain about every 2 seconds for a period of several minutes, usually while the person performs some mental task. The images are acquired in a manner that is sensitive to the blood oxygen-level dependent (BOLD) signal. Through the use of signal processing principles, spatial transformations, and statistical techniques, this time series of images is used to localize brain regions where the BOLD signal is higher or lower, providing insight into which parts of the brain were more or less metabolically active. The BOLD signal is the key measurement from fMRI, as it reflects increased neuronal activity, though indirectly. The rationale is that greater neural activity must occur where there is greater demand for oxygen (Logothetis, 2003). Usually "activation" via a BOLD signal measurement is meant as "relatively active" compared to some control task. It is also considered relative to the

background "noise" of the brain conducting its constant business of homeostatic and other regulatory processes, taking in external stimuli, blocking out irrelevant signals, and, of course, conscious thought (appreciation of this constant activity in the brain negates any serious consideration of the axiom "humans only use 10% of their brain" (Beyerstein, 2004)). Further, it would be a mistake to think of parts of the brain not identified as "active" during some task to be *non*-active for that task; they may simply not be differentially active in a key manner for the purposes of the study. For example, the primary visual cortex of the occipital lobe at the back of the brain becomes active when a person views emotional faces. However, the occipital lobe is not differentially active across emotional expressions and so is not reported as "active" in such studies. Usually the interest is in what may be uniquely active within the brain during viewing of, for example, threatening faces.

A great deal of methodological and technical creativity has gone into fMRI studies to capture brain activity during experimentally controlled cognition or behavior. Subjects may passively view stimuli, such as pictures, many of which have become standardized sets used by multiple research groups. Subjects may perform mental operations such as judging similarity of objects, silently repeating words, or imagining a scene in accordance with a script read to them. In addition to showing stimuli in the scanner to monitor the brain as it processes input or conducts a mental task, responses documenting answers or judgments can be recorded during scanning, serving as external indicators of thought. This recording is conducted via a number of MRI-compatible human–computer interface devices such as button boxes located at the fingertips, eye movements recorded via eye trackers, and more. All of this is implemented in a context of also requiring the participant to lie as still as possible while being scanned.

A final type of neuroimaging to mention is positron emission tomography (PET), which arguably can convey either functional or structural information about the brain. This technique relies on measuring properties of radioactive materials injected intravenously, so as a method, has practical limitations. However, it predated fMRI as a means for assessing how different brain areas become "active" under different behavioral conditions or between different groups. PET has therefore provided some of the evidence regarding key brain areas underlying aggression. "Activation" in PET is defined by relative increases in metabolic demand in different brain regions. Although fMRI has surpassed this type of PET imaging in terms of safety and in terms of spatial and temporal resolution, PET has a unique capacity to convey molecular information about the brain, and so is a form of structural imaging. Through the use of different radioactive ligands specifically designed to detect the

presence or availability of neurotransmitters (chemical messengers facilitating communication from one neuron to the next) or their receptors, PET is able to measure these molecular features of the brain and to do so with regional specificity (Nasrallah & Dubroff, 2013).

The field of research neuroimaging is relatively young, but now mature enough to retrospectively recognize challenges in its past associated with its youth. Issues include small samples, poor statistical control, and other factors that limit scientific rigor (Poldrack et al., 2017). This understanding helps explain inconsistencies in the literature. There is increasing attention to the need for the field to develop and enforce standards for methods and reporting them (Carp, 2012). Awareness of such concerns will be critically applied wherever possible in the subsequent sections.

Neural Substrates of Human Aggression

A basic framework for understanding how human brains produce aggressive behavior draws from the principal observation that phylogenetically conserved motivational brain systems come under greater control as animals become more behaviorally complex. Aggressive behavior is observed across many species, including those with much simpler brains than mammals (let alone humans). Control and modulation of aggressive behavior in mammals comes by way of one of the distinguishing anatomical features of this group—the neocortex. Mammals possess this large outer layer of brain tissue in proportionally larger and more complex connectivity profiles as behavior becomes more complex, and in particular, more social (Barton, 1996; Hofman, 2012). The fact that there are complex control mechanisms in human brains regulating aggression fits with the dimensional nature of aggression as a human behavioral characteristic. Aggression is commonly observed but at varying frequency or intensity among individuals, and this range is related to the variety of factors impacting whether aggression occurs, including those internal to the person (traits, motivational state) or external (social or other environmental). From this array, a useful focus for this chapter is on key constructs known to contribute to the problematic impulsive aggression of IED. These are internal factors and include social–emotional information processing and relevant behavioral traits predisposing toward aggression (e.g., tending toward "approach" responses rather than "avoidance" responses across a variety of situations). These factors are mediated most clearly by three key brain regions: the amygdala, the

orbitofrontal cortex, and the temporoparietal junction. We discuss each in turn as follows, highlighting structural and functional neuroimaging studies supporting their roles first in healthy individuals and then in IED.

Studies of Healthy Individuals

Amygdala

The amygdala shows significant responsivity to negative, especially threatening, stimuli. In this way, it plays a role in aggression by signaling emotional provocation. The amygdala is a group of nuclei located bilaterally in the anterior medial temporal lobe. It is "corticoid" rather than cortical, meaning it does not show the organized cellular layering characteristic of neocortex. As nonneocortex, the amygdala has identifiable analogs in submammalian groups like lizards (Medina, Bupesh, & Abellan, 2011), and for our purposes here, represents that part of evolutionarily conserved brain systems for motivated behaviors such as aggression. Each nucleus in the human amygdala has its own connectivity profile with other parts of the brain, but when taken together, the connections paint a picture of the amygdala's role. It integrates external sensory information (such as threatening facial expressions), aspects of the internal milieu (such as current arousal state), and memory (knowledge of what is threatening), and influences behavior accordingly (Price, 2003).

Some evidence supports a correlation between structural properties of the amygdala such as its volume and propensity toward aggression among healthy people, though this is not always found. One small study of 20 healthy women reported greater history of lifetime aggression associated with smaller amygdala volumes (Matthies et al., 2012). This study was conducted using manual tracing of the amygdala size from MRI images. As opposed to these positive findings associating amygdala and aggression, no association of amygdala volume was found with life history of aggression in a large population-based community sample (Coccaro et al., 2018). This latter study employed a "voxelwise" search for such associations across the whole brain, meaning the whole brain was divided into $2 \times 2 \times 2$ mm cubes, or voxels, with each voxel assigned a value representing estimated density of gray matter within it, calculated with automated methods as part of a technique called voxel-based morphometry (Ashburner & Friston, 2000).

Another study of amygdala size addressed the nature of the structure as a subdivided set of nuclei serving different roles in aggression (Gopal et al., 2013). In this study, hand-traced volumes of the whole amygdala were not associated

with aggression or impulsivity. However, when amygdala traces were divided into a dorsal (top) half and a ventral (bottom) half, significant associations with variables of aggression were observed. Smaller left dorsal halves, thought to be influenced by the size of the central nucleus of the amygdala with outputs to the autonomic nervous system (internal milieu/stress), were associated with greater life history of aggression scores. The ventral half, presumably influenced largely by the size of basolateral nuclei of the amygdala where sensory input is received, associated bilaterally with motor impulsivity measures, displayed no relationship with aggression. This implies that the dorsal portion of the (left) amygdala may have more relevance to aggression through its impact on the autonomic nervous system, such that a smaller volume may lead to reduced regulation of stress responses induced by the autonomic nervous system. A key caveat for this study is that the sample contained 41 psychiatric patients with aggression scores in the problematic range; however, the diagnoses of the subjects were not those of usual interest to aggression research (i.e., many had psychotic and mood disorders rather than IED, psychopathy, or personality disorder).

Studies of the functioning of the amygdala in healthy groups have been far clearer than structural imaging in establishing the structure's role in aggression. Interestingly, straightforward studies in healthy populations have been more recent, following up on hypotheses about the role of the amygdala generated from animal, lesion, and clinical studies (including of IED, reviewed later in this chapter). These amygdala function studies have largely utilized fMRI, consistent with their recency, and the majority tend to employ tasks of viewing standardized faces making threatening facial expressions. Specifically, the faces are usually expressing anger or fear and are gazing at the camera. Angry faces are considered a less ambiguous social threat and therefore brain responses to them are of clearer interpretive value in understanding the role of a provocative threat in aggression. Fearful faces are more ambiguous, as they may indicate a variety of potential circumstances, yet are also informative for aggression research given the potential indication that fearful faces signal the need to prepare an aggressive response.

Carlson and colleagues conducted an fMRI study with 15 male and female healthy volunteers and found left amygdala response to very briefly presented fearful faces was stronger for those who reported more anger expression (Carlson, Greenberg, & Mujica-Parodi, 2010). This is consistent with one role of the amygdala as a rapid threat detector via its capacity to receive sensory input so brief that it may not be fully consciously processed. Such a rapid pathway for detection of threat is an important survival mechanism. These results are consistent with this aspect of the amygdala's role,

such that those with more sensitive amygdala responsiveness to rapidly detected threat are experiencing more instances of registering threat and therefore responding aggressively. This amygdala activation did not correlate with reported levels of experienced anger. On the other hand, right amygdala response was reduced when viewing fearful faces that were presented for longer periods of time, and so were fully consciously processed. This right amygdala response did correlate with greater propensity to experience anger. This association of lower amygdala response to fully processed emotional information and higher trait anger levels is consistent with reports of hypo-responsiveness of the amygdala in association with premeditated (as opposed to impulsive) aggression (Marsh & Blair, 2008).

Beaver and colleagues imaged 22 healthy people with fMRI and assessed a trait called "behavioral approach," a general pattern of lifelong behavior, or trait, associated with greater likelihood for aggression. They also assessed the opposite trait, behavioral inhibition, associated with lower tendency toward aggression. Left amygdala response to angry, but not sad, faces correlated with higher propensity for behavioral approach (Beaver, Lawrence, Passamonti, & Calder, 2008). The left-sided finding is consistent with that of Carlson et al. (2010), though both are small studies.

Carre and colleagues assessed only dorsal and ventral amygdala responses to threatening faces in relation to trait anger, anxiety, and gender in a robustly sized group of healthy individuals ($n=103$) (Carre, Fisher, Manuck, & Hariri, 2012). They found that while the whole group showed the expected amygdala response (encompassing both dorsal and ventral portions) to angry or fearful faces, men ($n=46$) with higher trait anger and higher trait anxiety (which correlate with one another significantly) had greater bilateral dorsal amygdala responsiveness to just angry faces, with a slightly more robust result for left dorsal amygdala. This finding further specified the role of left amygdala activation in response to threatening faces for men more likely to be aggressive. No such clear relationship of anger and amygdala activation to threat was found for women. Interestingly, gender is often used as a "covariate of no interest" in neuroimaging (or other) analyses when the sample includes men and women. This methodological step means that any differences in the activation to the stimuli that may exist between men and women is not examined, but is instead "tossed out" and analyses then move on to the construct of interest. Whether sex-specific effects would be found in other studies using this common covarying approach to gender is therefore unknown. However, it does seem likely sex effects would be found routinely if explicitly sought. This is for at least

two reasons: (a) behaviorally, men and women differ in propensity toward aggression (Archer, 2004) and (b) there is differential brain activity in accordance with sex hormone levels (Rubin et al., 2017) and menstrual cycle phase particularly impacting social cognition (Mareckova et al., 2014). If these factors were controlled for, clearer patterns may emerge for threat processing in women, but they are not commonly assessed.

Beyond threatening face processing, there is additional evidence from functional neuroimaging that supports the role of the amygdala in the normal range of aggression. One example is a social threat task conducted during fMRI scans in an all-female healthy sample ($n = 36$) involving playing a game against an opponent (Buades-Rotger, Beyer, & Kramer, 2017). The subject could choose to fight or flee when the perceived opponent was either highly provocative (aggressive) toward them, or less so. Results were that amygdala activation was only noted when fleeing a highly provocative (threatening) opponent. Amygdala activation was not identified as uniquely involved in a choice to "fight" the opponent. This sheds some light on threat signaling rather than participation in aggression per se for the amygdala. As the sample was restricted to females, further study is needed to determine whether men would show a similar result.

Frontal Cortex

The frontal cortex plays an important role in key aspects of impulsive aggression. It regulates amygdala responsivity, and participates in social information processing in a variety of ways, such as holding representations of reward/punishment valuations and mediating impulsivity. Whereas the amygdala is identifiable across many species, neocortex is unique to mammals, and the frontal portion is particularly developed in primates (Kass, 2013). Frontal cortex is comprised of functional portions that do not necessarily respect the obvious physical, anatomical boundaries provided by the gyri and sulci. Instead, these functional zones, identified via early cytoarchitecture studies and recent neuroimaging studies (Petrider, Tomaiuolo, Yeterian, & Pandya, 2012) span adjacent portions of different frontal gyri and are usually referred to with directional labels such as "medial prefrontal" or "dorsolateral prefrontal" cortex. These functionally unified zones spanning across frontal gyri portend the complex connections of frontal cortex within itself and with the rest of the brain, working to regulate and integrate demands from the outside environment and internal goals and motivations, such as it does in mediating aggression.

There are several portions of frontal cortex key to determining normal aggression, but most focus has been on orbitofrontal cortex (OFC) due to its anatomic and functional connection to the amygdala (Ghashghaei, Hilgetag, & Barbas, 2007). OFC is located across the orbital surface of the frontal lobe, the portion at the base of the front of the brain located over the eyes (orbits). It can usually be usefully further divided into lateral and medial portions, both of which are involved in aggression. There is no clear evidence for structural characteristics of OFC, detectable with neuroimaging, relating to normal ranges of human aggression. For example, the population-based community sample study assessing gray matter volume correlates of life history of aggression scores found no relationship with OFC gray matter volume (Coccaro et al., 2018). Another study used DTI to address whether integrity of the white matter connecting OFC and amygdala related to levels of normal aggression by scanning 93 younger (age 18-30, mean 23) healthy males and administering psychometric and analog laboratory measures of aggression (Beyer, Munte, Wiechert, Heldmann, & Kramer, 2014). They found no relationship of the white matter between OFC and amygdala to aggression, nor did any white matter tract correlate with aggression in exploratory analyses. While this finding may seem counterintuitive given established anatomical connectivity of amygdala and OFC, the sensitivity of neuroimaging methods to detect properties that quantitatively relate to a normal range of behavior may be inadequate. Further, the functional connectivity of OFC and amygdala is not solely dependent on white matter, and DTI measures of white matter between gray matter structures have not been shown to have reliable association with fMRI-based measures of connectivity.

Functional neuroimaging has demonstrated the role of OFC in normal aggression. In contrast to amygdala studies, the literature on OFC's involvement with anger or aggression is older and includes PET imaging. This literature hones in on the experience of emotions, whereas in the amygdala literature, focus has been more on emotional information processing (e.g., processing facial expressions). One such study of emotional experience utilized an emotion induction technique during PET scanning, asking 18 healthy adults to think of events from their own past that evoked either anxiety, anger, or emotionally neutral memories (Kimbrell et al., 1999). Subjects also viewed pictures of faces depicting the desired emotion for each memory. Anger increased activity in left lateral OFC, as did anxiety, but anger also evoked relatively greater right lateral OFC activation compared to anxiety. Another study attempted anger induction during

PET scanning using personal narratives of the 8 male participants to induce the feelings (Dougherty et al., 1999). Increased left lateral OFC activation was found during anger-inducing memories. Yet another approach reported was to ask 15 healthy volunteers to imagine acting aggressively per a scene described to them by experimenters during PET imaging (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). They also scanned the subjects while imagining a nonaggressive but similar scene, attempting to control for general mental imagery processes. Results showed medial OFC having lower activity under an imagined "unrestrained" aggression condition relative to the nonaggression condition.

These PET studies show contradictory outcomes in terms of lower vs. higher activation in OFC during anger/aggression. This is likely related to the different tasks used, where personal memory vs. nonexperienced imagining likely invoked the frontal cortex in fairly different manners. Further, the computations involved to analyze the data, including contrasting the anger conditions against different kinds of control conditions, can result in conclusions of greater or lesser activation and are not straightforward to compare. However, OFC as key to experienced anger and aggression is a reasonable conclusion to draw on the basis of these studies.

One PET study examined emotional face viewing and reported OFC activation for viewing angry, but not sad, faces in 13 healthy males (Blair, Morris, Frith, Perrett, & Dolan, 1999). However, there was no amygdala response to angry faces. This, along with the lack of amygdala response in the emotion induction studies previously discussed, raises some concern for whether PET is as sensitive to anger-related change in the amygdala as it is for OFC. To some extent the PET method (e.g., choice of radioactive substance, design of stimulus presentation) may play a role in differential sensitivity.

Other paradigms of experiencing and enacting aggression in a healthy sample have been conducted in fMRI studies and further characterize the role of OFC. Beyer and colleagues had 32 healthy males being scanned while viewing videos of someone looking angry or neutral while also enduring provocative, aggressive actions by the person in the videos (e.g., using an adapted Taylor Aggression Paradigm) (Beyer, Munte, Gottlich, & Kramer, 2015). Medial and lateral portions of OFC were activated in association with viewing the angry faces and experiencing behavioral aggression. However, the more reduced the medial OFC activation was while viewing angry faces, the more aggressive the subject was when given the opportunity. Curiously, the amygdala did not show any differential responsivity

to any task condition. Another study of experiencing aggression by another person in an experimentally controlled manner with the chance to act aggressively back (Skibsted et al., 2017), conducted in twelve females and eight males, also found OFC activation when being provoked, as well as increased amygdala response. However, the task, smaller sample size, and/or analysis approach did not prove sensitive enough to reveal any brain regions associated with choosing to respond aggressively.

Functional connectivity, or correlated fluctuations in activity over time, is of interest for OFC and amygdala to better understand their roles in aggression. In one study, connectivity was assessed from fMRI scans acquired while healthy males ($n = 13$) engaged in violent and nonviolent acts in a video game, a potential analog to engaging in aggressive behavior (Klasen et al., 2013). The amygdala-OFC connectivity was further compared while the participants took a placebo or quetiapine, a drug known to reduce aggressive behavior. The subjects reported lower feelings of anger and aggression while taking quetiapine compared to placebo, and OFC-amygdala connectivity was reduced during aggressive acts compared to nonviolent acts in the game while taking the quetiapine. This suggests that altered synchrony between the two regions may be a mechanism of this medication-induced reduction in anger and aggression.

Other Prefrontal Cortical Areas

We have noted the lack of amygdala and OFC brain volume correlates with aggression in a population-based community sample. Despite this negative finding, the investigators did report that gray matter volume in medial prefrontal and lateral prefrontal cortex correlated inversely with a greater life history of aggression (Coccaro et al., 2018). This suggests that the role of these cortices may be more important in the normal range of aggression than is appreciated in the literature that focuses on amygdala and OFC, which largely stems from clinical studies. Similarly, in a study of self-reported healthy young adults ($n = 138$), which similar to Coccaro et al. (2018) searched the whole brain for correlation between aggression and gray matter density, lower gray matter in medial prefrontal cortex correlated only with the proneness for physical (but not verbal) aggression (Chester, Lynam, Milich, & Dewall, 2017). Finally, an fMRI study of healthy individuals (8 female, 10 male) reported reduced medial prefrontal gyrus activation during anger induction, but not during anxiety induction, offering some functional insight into the role of the more dorsal medial frontal region

(Kimbrell et al., 1999). Overall, further work is needed to clarify the role of these prefrontal regions in the normal range of aggression.

Temporoparietal Junction

A final key brain area for aggression may be the temporoparietal junction (TPJ), a portion of neocortex located, as the name implies, at the junction of two lobes, the temporal and the parietal. It is thought to support functions such as distinguishing self from other, and "mentalizing," or understanding the thoughts, feelings, or perspective of others (Carter & Huettel, 2013; Eddy, 2016). Impulsive aggression could be mitigated or exacerbated on the basis of such information since attribution of hostile intent versus a more innocent attribution of action taken by another increases the risk of aggressive behavior toward the "other." While structural neuroimaging studies have not found TPJ to be associated with aggression in healthy individuals, one functional neuroimaging study has reported an association. TPJ was active in an fMRI study of healthy women ($n = 36$) engaging in a task where an opponent behaved more or less aggressively and the participants could fight back or flee (Buades-Rotger et al., 2017). Analyses indicated that the TPJ was activated when fleeing from high aggression, suggesting that such behavior is accompanied by heightened signaling regarding the understanding of the other person's intentions. Attention to this region is newer for human aggression research and further studies should continue to shed light on its role.

Intermittent Explosive Disorder

The behavioral nature of IED is extensively described elsewhere in this book. Briefly, it is a psychiatric condition diagnosed when aggression occurs at an abnormally high frequency and/or intensity, and is maladaptive. It is distinguished from other forms of problematic aggression, such as premediated aggression as may occur in psychopathy, by the reactive/impulsive nature of the aggressive acts. There have been neuroimaging studies of other psychiatric conditions where impulsive aggression is problematic, such as borderline personality disorder, known to have not only the aggressive behavior overlap, but also diagnostic overlap with IED. However, this overlap is not often formally assessed and reported in studies of borderline personality disorder, so it is not straightforward to apply the findings to IED. While such literature has been used to support hypotheses on neural alterations associated with IED, there is now a body of neuroimaging literature focused on IED that is directly informative and is the focus of the review below.

Amygdala

Alterations to structural properties of the amygdala have been found in IED. A straightforward study of gray matter volume across the entire brain in a sample of 57 people with IED found that, compared with 53 healthy people and 58 people with other psychiatric disorders, the right amygdala had reduced gray matter (Coccaro et al., 2016). Further, this study found a correlation showing less gray matter was associated with a more extensive history of aggressive behavior. The shape of the amygdala was also abnormal in roughly the same sample, with significantly more areas of inward deformation compared with healthy controls (Coccaro, Lee, McCloskey, Csernansky, & Wang, 2015), specifying further the nature of the altered amygdala structure in IED.

Neuroimaging studies addressing functional brain alterations in IED have focused on social threat processing. Viewing emotional faces expressing threat (anger and fear) has therefore been a centerpiece of these neuroimaging studies and reveals altered amygdala function. The first study directly observing subjects with IED ($n=10$) compared with controls used fMRI during emotional face viewing and found greater amygdala response to angry faces for those with IED (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Further, the more the amygdala showed this heightened reactivity to angry faces, the greater the extent of their prior aggressive behavior. Similar heightened response to angry faces in the amygdala was found in a larger ($n=20$) IED sample (McCloskey et al., 2016). The findings from these two studies are consistent despite their employing slightly different versions of the emotional faces tasks. The earlier study asked participants to identify gender of the emotional faces, rendering the emotional processing aspect implicit. The later study asked participants to label the emotions they were viewing as positive or negative, making emotional processing explicit. The observation of heightened amygdala response to angry faces in IED regardless of these task conditions suggests the heightened amygdala response is not impacted readily in IED by the higher order processes invoked by the different task instructions. Rather, the deficit appears to be a more bottom-up, sensory processing alteration.

One study reported on both structural and functional aspects of the amygdala in groups of men characterized as high on reactive aggression to a problematic degree (not formally a study of IED, but reasonably approximating it) (Bobes et al., 2013). Amygdala function was assessed with an emotional face processing task, using fearful or neutral expressions. The aggressive men had increased amygdala reactivity to neutral faces and less

gray matter in left dorsal amygdala. These functional and structural findings overlapped in location. These abnormalities were also correlated with self-reported reactive aggression, such that greater abnormality in amygdala associated with greater aggression, and the amygdala abnormalities did not correlate with callous traits as seen in conditions associated with premeditated aggression. The heightened response to neutral faces is similar to prior reports of aggressive individuals perceiving neutral faces more negatively (Best, Williams, & Coccaro, 2002). Lack of heightened reactivity to fearful faces is consistent with the Coccaro et al. (2007) study, which used fearful faces but did not find significantly increased activity for them in IED.

Orbitofrontal Cortex

The only study addressing OFC size in IED was the Coccaro et al. (2016) study, which employed a whole brain search for gray matter differences between IED, healthy and psychiatric controls. Findings included reduced OFC volume in IED. OFC was also part of the composite measure, along with amygdala and other regions, which correlated negatively with severity of aggression (smaller volume associated with greater aggression).

The first study of IED subjects viewing emotional faces (Coccaro et al., 2007) found reduced OFC activation for angry expressions compared to controls. Further, healthy controls demonstrated a negative correlation between left amygdala and OFC activation during this task, whereas IEDs did not show any correlation between those regions. While the later study with a larger IED sample (McCloskey et al., 2016) did not report OFC activation differences between IEDs and controls for anger or any expression, assessment of right amygdala connectivity to OFC did show alteration. Controls displayed a negative correlation, as in the earlier study, but IED subjects displayed a positive correlation between the brain regions. While these smaller studies have inconsistencies, they both fit a hypothesis of a dysregulated circuit between the highly interconnected amygdala and OFC for processing and regulating responses to threat.

A PET study assessing receptors for the neurotransmitter serotonin sheds some light on how results of functional neuroimaging studies of IED may be inconsistent in OFC: they could be due to state-dependent effects. Specifically, the state-dependent effect could be how recently aggressive behavior occurred. The finding was that IED ($n = 14$) subjects with at least three acts of physical aggression in the past year had lower serotonin levels in the OFC compared with IED subjects without such recent aggression and compared

with healthy controls (Rosell et al., 2010). Hence, the recency of aggression in IED may be reflected in aspects of OFC physiology. When OFC function is normal in some studies, it may be due to a preponderance of subjects without such recent aggression history. On the other hand, serotonin receptor binding measured in PET has unclear association to the BOLD signal measured in fMRI studies, so these are tentative interpretations and further research is needed. However, other PET studies have found reduced serotonergic modulation in OFC in impulsive aggressive individuals (New et al., 2002; Siever et al., 1999).

Another study of potential, though indirect, evidence for reduced OFC function in IED involved nine individuals convicted of murder or attempted murder, and whose crimes were described as uncontrolled, emotionally charged, and who were described as individuals who could generally be triggered by physical or verbal aggression from others (Raine et al., 1998). These "affective murderers" were compared with murderers whose crimes were predatory/premeditated. The comparison was on brain metabolism as assessed with PET imaging while performing an attention task. Results showed lower lateral and medial prefrontal metabolism for the affective murderers. All murderers had increased subcortical metabolism (amygdala, midbrain, hippocampus, and thalamus). Hence, those with unplanned impulsive violence were characterized by lower function in frontal brain regions thought to normally inhibit and modulate limbic regions, including those subcortical areas showing increased metabolism.

Other Frontal Cortex

There are additional areas in the frontal cortex that appear to be structurally altered in IED that are relatively recent observations and require further study. In the population-based study of brain volume and aggression referred to earlier, about 10% of the subjects reported elevated life histories aggression, similar to the level observed in those with IED. This subgroup displayed a 10% reduction in both the medial prefrontal cortex and the left lateral prefrontal cortex (Coccaro et al., 2018). A study of white matter integrity, as assessed via DTI, was conducted in those with IED ($n=42$) compared with psychiatric (but nonaggressive) controls ($n=42$) and healthy controls ($n=40$) (Lee et al., 2016). Results were that IEDs had reduced white matter integrity in portions of a major white matter tract called the superior longitudinal fasciculus, connecting frontal and temporoparietal regions. The location of the alterations to this large tract was fairly central,

potentially contributing to disruption in long-range communication from frontal to posterior and temporal regions. Further, these reductions in white matter integrity correlated with worse aggression. Such problems with communication across the brain's major regions may help explain altered functional activation and behavioral disturbance, as there could be less optimal regulation and information integration given a degraded communication conduit.

Temporoparietal Junction

No study, to date, has reported changes in TPJ volume or other structural aspects in IED, though the white matter alterations noted in the Lee et al. (2016) study could certainly impact connectivity of TPJ to other areas. One functional imaging study has implicated TPJ as a potential location of change associated with medication known to reduce aggression in IED (Cremers, Lee, Keedy, Phan, & Coccaro, 2016). The study used an emotional face processing task during fMRI. Subjects took either escitalopram, a selective serotonin reuptake inhibitor (SSRI), or placebo. A primary finding was that IEDs ($n=17$) had increased activity in TPJ while taking escitalopram and viewing a variety of emotional faces compared to controls ($n=14$) and to placebo. This was observed in the absence of change in the amygdala in IED. This location of enhanced neural function associated with the SSRI in IED could impact perspective taking or more accurate assessment of others' minds, though these constructs were not measured in the study. Overall, this enhancement to social cognitive processing is a potential therapeutic approach for IED.

Conclusion

Neuroimaging studies spanning structural and functional methods support a model specifying some key neural substrates underlying normal human aggression and problematic impulsive aggression as exemplified by those diagnosed with IED. These brain regions include the amygdala, with its rapid threat-detecting properties particularly tuned to social threat, and the OFC, which regulates the amygdala and appears to play a role in the experience of anger as well as social threat processing and responding. IED is associated with alterations in these brain regions. Additional portions of the frontal lobe and the TPJ are emerging as having key roles, as well, for aggression and its regulation, with TPJ of particular interest as a treatment target. Overall, this picture is consistent with the complex nature of

neurocognitive determinants of human aggression, as well as with the relative newness of neuroimaging methods in research, yielding some converging evidence, but some that is in need of further, more rigorous study.

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