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BEHAVIORAL DISSOCIATION OF ORBITAL/MEDIAL AND DORSOLATERAL FRONTAL LOBE FUNCTIONING IN PATIENTS WITH INTERMITTENT EXPLOSIVE DISORDER

Dissertation

Presented to

The Faculty of the School of Health Professions

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In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

by

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Department of Clinical and Health Psychology

March, 2000

SCHOOL OF HEALTH PROFESSIONS

THESIS APPROVAL

This is to certify that the thesis presented to us by Mary Best

on the 29th *day of* March, 2000, *in partial fulfillment of the requirements for the degree of* Ph.D. *in the* Clinical & Health Psych. *Program has been examined and is acceptable in both scholarship and literary quality.*

COMMITTEE MEMBERS' SIGNATURES

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ABSTRACT

Aggression can be defined as an intense, harmful, and hostile action taken against oneself, another person, or an object. Aggression can be expressed verbally, indirectly or directly to another person. The DSM-IV has only one disorder with aggressive behavior as a primary symptom, Intermittent Explosive Disorder (IED). Criteria for IED include several episodes of impulsive aggressive behavior out of proportion to provocation. To date no study has examined the neuropsychological profile of subjects with IED.

Humans and animals with lesions to the orbital/medial prefrontal cortex and associated limbic brain areas display impulsive aggressive behavior. Associated cognitive and perceptual deficits include emotional misperception, disinhibition, and impaired smell identification. The goal of the present study was to test the hypothesis that subjects with IED would have a cognitive profile similar to patients with lesions to orbital/medial prefrontal cortex. Subjects with IED (N=24) and age-, education-, and IQ-matched control subjects (N=22) were given tests of facial expression identification, response inhibition, and smell identification. These tests have been linked to the integrity of the orbital/medial prefrontal cortex. To determine specificity of prefrontal dysfunction, subjects were given control tests of working memory linked to the dorsolateral prefrontal cortex.

Subjects with IED performed significantly worse than controls on the three orbital/medial tasks. Subjects with IED were impaired at identifying negative facial expressions and showed a bias to label neutral faces with a negative expression. IED subjects had difficulty learning associations and correctly altering their behavior in response to punishment in a simulated gambling task. They were also impaired at identifying odors. Subjects with IED performed similar to controls on the dorsolateral control tasks of working memory.

Subjects with IED showed a pattern of impairments that resembled impairments in patients with orbital/medial prefrontal cortex lesions. However, the degree of impairments in IED was milder than patients with lesions. This study provides evidence for a mild dysfunction in orbital/medial prefrontal cortex in IED. This study has implications for psychotherapeutic interventions in IED. Future studies could more directly test the orbital/medial hypothesis in IED by functional neuroimaging of prefrontal cortex while subjects perform tests investigated in this study.

DEDICATION

I dedicate this dissertation to a man who is, at once, my love, my best friend, my mentor, my cheerleader, and my clown. Thank you for sharing this with me. To my husband, Jonathan Demb.

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INTRODUCTION

A Definition of Aggression

A widely accepted definition of aggression first proposed by Moyer (1976) states that aggression is "an overt behavior involving intent to inflict noxious stimulation or to behave destructively toward another organism." The object of aggression is limited to a person or animal but it may also include an inanimate object if "frustrating or aversive stimulation is involved." This definition is too vague to be useful for classifying an individual in a research study. For subject classification, a more specific definition of aggression and its many manifestations is required.

Coccaro (1995) provides a more specific definition of aggression that is especially useful for the purpose of categorizing individuals for research studies. A label of "aggressive behavior" requires that the aggressor take an "intense, harmful, and hostile action against himself, another person, or an object." There are three basic forms of aggression: verbal, indirect and direct. Verbal aggression refers to a vocal expression of anger used to punish, threaten, or humiliate another person. Indirect aggression refers to an attack on an inanimate object (e.g. punching a wall). Direct aggression refers to a direct, physical attack on a person or animal. Direct aggression also refers to self-directed aggression, including suicide.

Coccaro (1995) further divides aggressive acts into three forms: defensive, predatory, and impulsive. Defensive aggression occurs in response to a real threat to an individual or an individual's family or friends. This form of aggression is commonly associated with "self-defense". For example, a soldier in a combat situation often displays defensive aggression. Generally, this form of aggression is not considered pathological.

Predatory aggression involves premeditation and the consideration of the possible rewards of committing an aggressive act. Aggression in this context is a vehicle towards satisfying the aggressor's needs. Predatory aggression is considered pathological, but it is not defined as a specific disorder in the Diagnostic and Statistical Manual of mental disorders, fourth edition (DSM-IV, 1994). Instead, it is generally expressed as a symptom within a broader disorder such as Antisocial or Borderline Personality Disorder.

Impulsive aggression is triggered by the individual's emotional frustration with stimuli in the environment. Impulsive aggression is the only aggressive behavior that warrants a diagnosis in the DSM-IV, referred to as Intermittent Explosive Disorder (IED). Impulsive aggression as it relates to IED, will be the focus of the present study.

Aggression as a Clinical Disorder

Diagnosis of Intermittent Explosive Disorder (IED)

IED is categorized in the DSM-IV (1994) as one of the "Impulse Control Disorders not otherwise specified." In order to receive a diagnosis of IED several criteria must be met. First, there must be several episodes of "a failure to resist aggressive

impulses that result in serious assaultive acts or destruction of property." The inclusion of this first criterion suggests that the aggression must be impulsive rather than premeditated. The second criterion states that the "degree of aggressiveness expressed during the episodes is grossly out of proportion to any precipitating psychosocial stressors." This second criterion implies that the aggressive behavior is unjustified given the circumstances. The third criterion states that several other disorders must be ruled out: Antisocial Personality Disorder, Borderline Personality Disorder, a Psychotic Disorder, a Manic Episode, Conduct Disorder, and Attention-Deficit/Hyperactivity Disorder. Two other rule-out criteria are substance abuse and a general medical condition such as a traumatic brain injury.

History of the Diagnosis of Intermittent Explosive Disorder (IED)

IED was not a formal disorder until DSM-III was published in 1980. In the first DSM such symptoms would have been captured under the personality disorder Passive Aggressive Personality Disorder, Aggressive type. The DSM-II added Epileptoid Personality Disorder (EPD) which was characterized by "gross outbursts of rage or of verbal or physical aggressiveness". Individuals with this diagnosis were thought to be unable to control their aggressive outbursts. The DSM-II also included a related disorder called Isolated Explosive Disorder, that was characterized by extreme, "catastrophic" aggressive outburst that only occurred one time (DSM-II, 1968)

Between the publication of the DSM-II and the DSM-III, Monroe (1970) published an elaborate nosology and classification of episodic disorders. Monroe offered evidence that these disorders involved seizures in the limbic system. Mark and Ervin (1970) expanded on Monroe's ideas and included four criteria for the "episodic

dyscontrol syndrome": 1) physical assault, 2) pathological intoxication, 3) impulsive sexual behavior, and 4) numerous traffic violations and accidents.

In response to these new theories, the DSM-III replaced Epileptoid Personality Disorder with Intermittent Explosive Disorder (DSM-III, 1980). IED diagnosis criteria were: 1) several discrete episodes of loss of control of aggressive impulses that result in destruction of property, 2) degree of response is out of proportion to the provocation, and 3) genuine regret or self reproach follows the episode. In this version of the DSM-III, only organic factors such as epilepsy were considered as etiological causes of the disorder (DSM-III, 1981).

The revised version of the DSM-III (DSM-III-R, 1987) added exclusionary criteria for IED diagnosis, such as "not better accounted for by a psychotic disorder, organic personality disorder and intoxication with a psychoactive substance." The category, Isolated Explosive Disorder, was deleted from this version of the DSM (DSM-III-R, 1987). The DSM-IV did not add any significant changes to the IED diagnosis.

While the gender distribution of IED is clear, 80% male (DSM-IV sourcebook, 1994), the prevalence rate remains controversial. The DSM-III and DSM-III-R refer to IED as a "rare" disorder. For example, Felthouse (1991) found that out of 443 men who responded to an advertisement recruiting individuals who identified themselves as "having a problem with anger", only 18.9% met criteria for IED. However, Coccaro (personal communication) suggested that the prevalence rate could appear to be rare because of overly restrictive and poorly defined diagnostic criteria.

Felthouse (1991) characterized several aspects of aggressive behavior in male patients with IED. Individuals with IED reported that they were most often "provoked"

by a person close to them such as a spouse or girlfriend. Aggression almost always occurred immediately after these perceived provocations. Individuals with IED denied that the outbursts were premeditated. The men reported that they were generally alert and oriented during outbursts, and most had at least partial memory of the event.

Controversies Surrounding the Diagnosis of IED

The current diagnosis of IED remains controversial. Felthouse (1991) has called the criteria for IED "poorly operationalized." Coccaro (1998) has also criticized the current criteria for an IED diagnosis on several grounds. One major criticism is the "unrealistic exclusion criteria". The DSM-IV excludes individuals with a diagnosis of Borderline Personality Disorder (BPD) and a diagnosis of Antisocial Personality Disorder (APD). These exclusion criteria exist because both BPD and APD sometimes include features of irritability, anger outbursts, or aggressive behavior. The authors of the present DSM-IV criteria included these rule-outs because they did not want to over-diagnose IED.

However, a problem with this strategy is that APD and BPD are not homogeneous disorders. For example, only a percentage of patients diagnosed with BPD or APD have aggressive or impulsive traits (Coccaro, 1998). Coccaro (1998) found that 78% of subjects with a diagnosis of BPD met criteria for IED, and 58% of individuals with a diagnosis of APD met criteria for IED. In addition Coccaro (1998) contends that regardless of the BPD or APD diagnosis, symptoms of impulsive aggression may be clinically relevant in terms of a treatment response. For example, Coccaro et al. (1989) found that pharmacological treatments selectively decreased symptoms of impulsive aggression in individuals with diagnoses of APD and BPD and had no effect on other

symptoms associated with these disorders. Finally, there is no data to support the hierarchical exclusion of IED for BPD or APD (Coccaro, 1998).

Coccaro (1998) has also pointed out that the present inclusion criteria are poorly operationalized. For example, there is no elaboration of what "serious assaultive behavior" constitutes. Does a push constitute serious assaultive behavior or must there be a more severe punch or kick? Many individuals who commit "less severe acts of assaultive behavior" can nonetheless have ramifications in their lives that produce significant distress (8, Kavoussi, Berman, Weinberg, & Lish, 1999). This suggests that rather than the degree of assaultive behavior, the distress caused by any degree of assaultive behavior may be most relevant.

A similar problem relates to the definition of "destruction of property". Does this criterion refer to any inanimate object, or just objects worth a certain value? These questions are left unanswered in the current DSM-IV. In addition, unlike most diagnoses in the DSM-IV, there are no frequency guidelines to establish how often these behaviors must occur to be considered pathological. The lack of clarity that surrounds this diagnosis makes classification of individuals for research very difficult. At the same time, research in this area is critical to our understanding and treatment of the disorder.

Therefore research on impulsive aggression requires a modified version of the IED diagnostic criteria. Coccaro (1998) has made significant revisions to the current DSM-IV criteria in order to address some of the identified problems. In contrast to the DSM-IV criteria, Coccaro (1998) specifies that the aggression can be either "verbal or physical aggression" directed at other people, animals, or property. This first revision broadens the scope of the diagnoses while clarifying the nature of the aggressive act. A

second revision is the inclusion of a "distress" criterion. Coccaro's states that "the aggressive behavior causes either marked distress (in the aggressor) or impairment in occupational or interpersonal functioning." This revision is intended to bring the IED diagnosis in line with other Axis I diagnoses that usually include this kind of stipulation.

Coccaro (1998) also eliminates some of the rule-out diagnoses and includes only: Mania, Major Depression, and Psychosis, as well as the standard rule-out criteria for general medical condition or substance abuse induced aggression. He adds a rule-out criterion for Late Luteul Phase Dysphoric Disorder and stipulates that the "the aggressive behavior does not occur exclusively during the late luteal/premenstrual period."

Coccaro's (1998) final revision is an inclusion of frequency and time criteria. The criteria are that "[the] aggressive episodes occur either an average of twice a week for four weeks, or at least eight times per month, for at least a period of one month currently or in the past." This is also intended to bring the diagnosis more in line with other Axis I diagnoses that usually include a time frame. The revised version of the IED criteria, referred to as "IED by research criteria", has shown good construct validity, discriminant validity, and inter-rater reliability (r = .92) (Coccaro, Kavoussi, Berman, & Lish, 1998).

The Etiology of Aggression

Psychosocial Factors

To date no study has addressed the psychosocial factors which are specifically related to the development of IED. However, Dodge and his colleagues have published studies on adolescents who exhibit two of the more important features of the disorder,

impulsivity and aggression. These adolescent studies may provide some insight into some of the psychosocial factors relevant to IED.

Dodge and his colleagues divide aggressive adolescents into "reactive aggressors" and "proactive aggressors" (Dodge, Lochmann, Harnish, Bates, & Pettit, 1997). Reactive aggressors display attacks of "hot-blooded" anger. These attacks occur in response to the smallest threat, and individuals show little self-control over their negative emotions. Proactive aggressors display attacks of "cold-bolded" anger. These attacks are organized towards a goal. Studies by Dodge et al. on reactive aggressors, described below, may well apply to adult IED patients since they share symptoms of emotional dyscontrol and impulsivity.

Consistent with other studies on the development of aggression (e.g., Huesmann, Eron, Lefkowitz, & Walder, 1984), Dodge et al. reported that early exposure to violence predisposes a child to act violently later in life (Dodge, Pettit, & Bates, 1994). Furthermore there were differences in how children classified as "reactively aggressive" and "proactively aggressive" were raised. The development of reactive aggression was associated with harsh discipline, exposure to aggressive adults, and lack of cognitive stimulation. In a later study, harsh discipline and child abuse (independent of income level) predicted behavior characterized as reactively aggressive but not proactively aggressive (Dodge et al., 1997). In fact 41% of this sample of children identified as having been abused during the first five years of life become high reactive aggressors later in life. In contrast only 15% of non-abused children became reactively aggressive. In contrast, not one of the proactively aggressive boys was abused (Dodge et al., 1997).

Dodge et al. have also reported differences in social information processing in reactively versus proactively aggressive children (Quiggle, Garber, Panak, & Dodge, 1992). In studies that focused on the attributional bias of aggressive children, aggressive boys, relative to non-aggressive boys, are more likely to attribute hostile intent to those interacting with them (Quiggle et al., 1992). However, these aggressive boys do not show this hostile attributional bias when they observe the same interaction between other children.

In other words, aggressive boys showed a situation-specific hostile attributional bias (Quiggle et al., 1992). Specifically, this bias only occurred in situations in which the actions and outcome are directed at the aggressive boy and excluded times when the boys were observing an interaction between others. In addition, aggressive boys with a hostile attributional bias were also more likely to report that they would retaliate aggressively towards those whose intentions they judged to be hostile.

Dodge et al. (1997) found that reactively aggressive children have more problems picking up on relevant social cues than do proactively aggressive children or non-aggressive children. Reactively aggressive children were more likely to incorrectly label a stimulus as "sad." In contrast, children rated as proactively aggressive, were more likely to expect that the commission of an aggressive act to a peer would lead to the reduction of aversive behavior by that peer. In addition, the proactively aggressive group had a greater sense of self-efficacy and self worth in social domains than the reactive aggressive group.

The work of Dodge et al. suggests that aggressive behavior is a life-long trait which negatively impacts the development of social skills. Repeating these experiments

with adult patients diagnosed with IED (reactively aggressive) and APD (proactively aggressive) would be quite valuable in tying together the child and adult literature on this subject. The work of Dodge et al. helps provide a context for the discussion of the biological variables that contribute to IED.

Biological factors

Genetics

Genetic studies have two basic experimental designs: twin studies and adoption studies (Carey, 1996). Most genetic studies of aggressive populations have been twin studies. Twin studies generally compare monozygotic (identical) twins with dizygotic (non-identical) twins. Greater similarity in monozygotic twins than in dizygotic twins implies a genetic basis for the behavior, because monozygotic twins share 100% of their genes, while dizygotic twins share about 50% of their genes. Coccaro, Bergeman, and McClearn (1993) found that specific aggressive behaviors such as the ability to inhibit aggression appear to be heritable. Five of 11 other twin studies also found evidence for the heritability of "hostile" aggressiveness (cited in Coccaro et al., 1993).

In another twin study, Coccaro (1997) found that self-reported assessments of assaultiveness and irritability are heritable. This study also reported that environmental factors that affected one or the other twin exclusively (such as developmental factors) accounted for more of the variance than environmental factors that affected both twins. In this study the effect of environmental influence was found to be greater than that of genetic influence. Environmental variables explained between 27-41% of variance in

regression models. These data suggest that genetic factors are significant predictors but explain only a minority of the variance associated with the development of aggression.

Neurochemistry

Many studies suggest that individuals with IED have a neurochemical imbalance. The neurotransmitter implicated in most studies is serotonin (5HT; Coccaro, 1995). The first studies to focus on the association of serotonin levels and aggressive disorders were conducted in the 1970's on animals (see Coccaro, 1995). Experimental manipulations that decreased 5HT levels in rats caused an increase in aggressive behavior. Conversely, drugs that increased 5HT levels decreased aggressive behavior. In addition, rats with low 5HT were hypersensitive to external stimuli that triggered aggressive behavior. These animals had lower thresholds of provocation for aggression (citations in Coccaro, 1995).

Human experiments have also found a relationship between low 5HT and impulsive aggression. In post-mortem brains, individuals who committed violent suicide, relative to depressed patients who did not commit suicide, had lower levels of a 5HT metabolite, 5HIAA (Asberg, 1976). Lower levels of 5HT were found in prisoners who had committed impulsive aggressive assaults compared with those who had committed premeditated assaults (Brown, Goodwin, Ballenger, Goyer, & Major, 1979). In a non-criminal population, impulsive aggression was also related to lower levels of 5HT (Linnoila et al., 1983). Low levels of the precursor to 5HT were found in violent alcoholics (Branchey, Branchey, Shaw, and Lieber, 1984). Individuals with impulsive aggression have a decreased number of 5HT receptor binding sites (Coccaro, Gabriel, & Siever, 1990).

These studies suggest that increasing 5HT levels could alleviate some of the symptoms of impulsive aggression. Increasing the precursor for 5HT metabolism (tryptophan) through dietary enrichment has been reported by some to decrease aggressive responding (Volavka, 1995). Coccaro, & Kavoussi (1996) report success in reducing the symptoms of IED, using fenflourimine, a selective 5HT reuptake inhibitor which effectively increases 5HT levels at a synapse. Based on the results of these experiments, these authors posit a model of impulsive aggression where a low 5HT level effectively decreases the threshold to act aggressively (Coccaro, & Kavoussi 1996). Individuals with decreased functional 5HT systems are therefore more likely to respond to perceived threat, frustration, or aversive circumstances with an aggressive outburst. The lower the functioning of the 5HT system the worse the outburst is likely to be. Therefore, these authors hypothesize that 5HT acts as a behavioral inhibitor. Coccaro, & Kavoussi (1996) also posit a hypothetical role for the neurotransmitters norepinephrine and dopamine in the perception of a stimulus as threatening and the activation of a cognitive or motor response.

General Evidence of Brain Dysfunction

Many individuals with IED show neuropsychological deficits. The DSM-IV sourcebook (1994) reported that a review of 258 articles and 30 books on this disorder revealed that many if not most subjects in the studies had some evidence of neurological impairment. Specifically, in the articles that examined these factors 55% of patients showed EEG abnormalities, 65% had abnormal neurological examinations, 59% had a history of seizures or head trauma, 58% showed impairments on neuropsychological tests, 38% had a history of learning disabilities, and 45% had a history of ADHD.