A Neuropsychiatric Perspective on Gambling and Morality

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Abstract: Public conceptions of the relationship between morality and gambling have changed over time. Emerging technologies involving brain imaging and molecular genetic approaches are providing insight into human behaviors including moral aspects of decision-making and behavior. These technologies are also facilitating an improved understanding of mental health conditions like pathological gambling. Data from these studies suggest that specific neural circuits are involved in "immoral" decision-making and disorders characterized by impaired impulse control (e.g., pathological gambling and substance use disorders). Additional identification and characterization of factors that contribute to excessive engagement in gambling will allow for improved public health strategies for pathological gambling.

Introduction

Evidence of gambling can be found across cultures and throughout time. Hebraic, Egyptian, Greek and Roman civilizations engaged in various forms of gambling (Quinn, 1892), and the Mahabharat, a central book of Hinduism, describes a gambler who wagers and loses his kingdom and his wife (Mahabharat, 1884).   The persistence of gambling for millennia suggests that the behavior may be particularly rewarding at an individual level or important in socio-cultural functions. Suggestion of the former can be found in work from over a century ago in Fyodor Dostoyevsky's *The Gambler* (Dostoyevsky, 1966). In this book as well as in his personal letters of the period (Dostoyevsky himself had a gambling problem), the thrill of gambling is poignantly described as an exciting and anxious state that his nature desires (Dostoyesvsky, 1998). The incorporation of gambling in social and cultural institutions (bingo sponsored by churches, lotteries sponsored by governments) also dates back centuries, with major institutions (e.g., Harvard University) originally founded in part with lottery proceeds. Thus, historical accounts suggest that complex reasons contribute to the societal maintenance of gambling.

Gambling and Morality

Morality has been defined as a doctrine or system of right, virtuous or ethical conduct (Miriam-Webster Dictionary, 2007). The term, derived from the Latin word *moralis*, initially described a consensus of manners or customs within a social group, and has been used throughout the past several centuries in efforts to identify universal principles that should guide the behaviors of humans (Moll et al., 2005a). Gambling has

been described as immoral for millenia. Greek philosophers like Aristotle are reported to have grouped gamblers with thieves and robbers and denounced gambling as wrong and immoral (Quinn, 1892). This sentiment was voiced in other cultures throughout time. In an article on the history of gambling published in England in 1756, gamblers are described as "cheats" and "felons", and the author states that society would be better off without this group of "harpies" (Fielding, 1756). Personal accounts of "degeneration" related to excessive involvement in gambling were described. In 1882, Mason Long described his personal struggles with excessive gambling, drinking and tobacco smoking, culminating in his religious conversion and confession of his sins (Long, 1882). Other works from the same time period similarly describe gambling as a sin or a vice (Talmadge, 1888; Conwell, 1892; Quinn, 1892). The relationship between individuals' emotional states (as described by Dostoyevsky above) and gambling appears to contribute to gambling being conceptualized as an immoral behavior. For example, when discussing in 1902 the moral qualities of gambling in *The Ethics of Gambling* (MacKenzie, 1902), the uncertainty about a wager "contributes largely to the gambler's pleasure, and it is around this that the emotions gather with such unnatural concentration so as to produce in some a kind of moral or spiritual inflammation which we call the gambler's craving or passion." (p. 40). That is, the seeking of an immediate reward in an emotional or passionate manner to the extent that it might interfere with family, work or other areas of functioning seems salient to the consideration of gambling as immoral. Over the past half century in the United States and elsewhere, individual liberties and the ability to make personal decisions about recreational and leisure activities have received high priorities. Within this context, legalized gambling has seen considerable expansion,

with legalized gambling estimated to have grossed approximately $85 billion in the United States in 2005 (American Gaming Association, 2006). As compared to prior conceptualizations of gambling (particularly when done in excess) as a sin or a vice, one current conceptualization of gambling involves a personal choice of a recreational activity within a public health framework (Korn and Shaffer, 1999; Shaffer and Korn, 2002), and when performed in excess a mental health condition (American Psychiatric Association 2000). Nonetheless, some of the same elements described over 100 years ago in relationship to gambling and morality (emotion and craving and their relevance to decision-making in gambling) are currently being investigated from neurobiological and medical perspectives.

Medical Model of Excessive Gambling: Pathological Gambling

The majority of adults gamble, with a minority demonstrating problems with gambling. The Gambling Impact and Behavior Study estimated that approximately two of every three adults in the United States had gambled within the past year, with less than 1% meeting the criteria for pathological gambling (Gerstein et al., 1999). Pathological gambling is the formal diagnostic term adopted by the American Psychiatric Association to define individuals who develop substantial problems related to their gambling. The disorder was first introduced in 1980 in the 3rd edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980) and is located in the category of "Impulse Control Disorders Not Elsewhere Classified". A central defining feature of the impulse control disorders is the "failure to resist an impulse, drive, or temptation to perform an act [e.g., gambling in the case of pathological gambling] that

is harmful to the person or others" (American Psychiatric Association 2000; Grant and Potenza, 2004; Williams and Potenza, in press). Typically "the individual feels an increasing sense of tension or arousal before committing the act and then experiences pleasure, gratification, or relief at the time of committing the act" (American Psychiatric Association, 2000). Guilt or regret may (or may not) be described following the act. In that the impulse control disorders as a group are characterized by a failure to resist temptation to engage in behaviors leading to immediate pleasure at the expense of other areas of life functioning, it is understandable that within a moral framework that they could be considered immoral.

The diagnostic criteria for pathological gambling share similarities with those for drug dependence. Both disorders have inclusionary criteria targeting tolerance, withdrawal, interference in major aspects of life functioning, and repeated unsuccessful attempts to cut back or quit (American Psychiatric Association, 2000; Potenza, 2006). Other criteria for pathological gambling appear more specific to gambling. For example, the criteria targeting "chasing" (returning to a gambling venue in an attempt to win back money recently lost) or "bail outs" (borrowing money to escape from a desperate financial situation related to gambling losses), although similar behaviors related to drug use are often exhibited by drug dependent individuals (Potenza, 2006). As such, pathological gambling has been conceptualized as a "behavioral addiction" or an "addiction without the drug" (Holden, 2001; Petry, 2006; Potenza, 2006).

Pathological gambling has also been conceptualized as lying along an impulsive-compulsive spectrum with disorders like obsessive-compulsive disorder (Hollander and Wong, 1995; Hollander and Benzaquin, 1996). The relationship between impulsivity and

compulsivity seems more complex than initially conceptualized (Grant and Potenza, 2006; Potenza, 2007a). In impulse control disorders and drug dependence, it is hypothesized that as use becomes compulsive in nature, brain regions involved in habit formation become increasingly involved in the psychopathology (Brewer and Potenza, in press). Impulsivity may predominate at early stages of the disorders and persist over time. As such, impulsivity, defined as a "predisposition toward rapid, unplanned reactions to internal or external stimuli [with diminished] regard to the negative consequences to the impulsive individual or others" is hypothesized to be a central element of pathological gambling and a broad range of psychiatric disorders that often co-occur with pathological gambling (Moeller et al., 2001; Petry, 2005; Potenza, 2007b). This definition highlights the complexity of impulsivity, and preliminary studies suggest that specific aspects (e.g., rapid reactivity and diminished regard to negative consequences) are not highly correlated and differentially related to treatment outcome (Krishnan-Sarin et al., 2007). As such, a more complete understanding of impulsivity and its core component features as they relate to pathological gambling should not only help improve our understanding of the disorder but also generate better prevention and treatment strategies. Investigations of neurobiological aspects of impulsivity and motivated behaviors in disorders characterized by impaired impulse control are providing significant insight into neural circuits that might be disrupted in these disorders and might represent important targets for novel treatments (Chambers et al., 2003; Kreek et al., 2005; Chambers et al., 2007; Potenza, 2007b).

Brain Biology and Moral Behaviors: The Case of Phineas Gage

Biological underpinnings for gambling were hypothesized over 100 years (France, 1902). Even earlier, a case study suggested the involvement of specific brain regions in the commission of seemingly immoral behaviors. In 1848, a railroad worker named Phineas Gage was described by his bosses as "the most efficient and capable" man whom they employed (p. 4) (Damasio, 1994). He displayed "temperate habits", had a "well balanced mind" and was "very energetic and persistent in executing all of his plans of action" (p. 8) (Damasio, 1994). In other words, Mr. Gage was a successful, hard-working, industrious young man. However, at 25 years of age, he encountered a horrible accident in which a steel tamping rod exploded through his left orbit and exited through the top of his skull. Miraculously, he survived the accident. However, he was no longer the same man: "Gage was no longer Gage." John Harlow, the physician caring for him after the accident, stated that the "equilibrium or balance, so to speak, between his intellectual faculty and animal propensities" had been damaged (p. 8) (Damasio, 1994). Gage became "fitful, irreverent" and indulged in "the grossest profanity which was not previously his custom" (p. 8) (Damasio, 1994). He displayed "little deference" for others and was "impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned" (p. 8) (Damasio, 1994). He was described as displaying "strong animal passions" and women were advised not to be near him due to his foul language and behavior (Damasio, 1994). His employers needed to let him go, noting that although he had the physical ability to perform his duties, his "new character" was incompatible with holding his job (Damasio, 1994). After 13 years of having difficulties holding a job, he died poor in 1861.

Biology of Decision-Making: Emotions and the Ventromedial Prefrontal Cortex

The tragic case of Phineas Gage provided a unique opportunity for exploration of brain regions and circuitry contributing to moral vs. immoral behaviors. That is, if one were to be able to identify the brain region(s) impacted by the tamping rod in the case of Phineas Gage, the information could generate insight into the neurobiological contributions to morality. Fortunately, the physician caring for Gage retrieved his skull and it is currently housed at the Harvard Medical School. By using the skull size and regions of skull damage to estimate the route of the tamping rod, three-dimensional images of the regions damaged in Gage's accident were generated (Damasio, 1994). Consistent with accounts of Gage after the accident, brain regions responsible for motor and language function were spared. However, frontal cortical regions, including the ventromedial prefrontal cortex, are believed to have been obliterated by the tamping rod. Antonio Damasio, Hanna Damasio, Antoine Bechara and colleagues pursued this finding further. As neurologists caring for individuals with strokes, they observed that people with stroke lesions in the ventromedial prefrontal cortex often did not fare well in real-life situations despite performing adequately on existing neurocognitive tests (Damasio, 1994). They developed a gambling test (the Iowa Gambling Task) to assess risk-reward decision-making and found that these individuals performed disadvantageously on this task (Bechara et al., 1994; Bechara et al., 1998). The task consists of selecting 100 cards from four decks. When performing this task, individuals are instructed to optimize gains with the understanding that some decks are better than others. Unbeknownst to the participant, two of the decks are associated with large immediate rewards and very large

intermittent losses resulting in long-term losses and the other two are associated with small immediate rewards and small intermittent losses resulting in long-term gains. As compared to healthy control subjects, those with strokes in the ventromedial prefrontal cortex perform disadvantageously on the task (select more cards from the decks with large immediate gains and very large intermittent losses that result in long-term loss). In these studies, individuals without stroke lesions would behaviorally learn the advantageous card selection strategy prior to being able to consciously report their strategy (Bechara et al., 1997). Subsequent studies implicated additional brain regions (e.g., the amygdala) as contributing to performance on the Iowa Gambling Task (Bechara et al., 1999). These findings, in conjunction with information on the role of the prefrontal cortex and amygdala in emotional processing, led to the somatic marker hypothesis of decision-making; namely, that emotional processes influence our rational decisions (Damasio, 1994).

Risk-reward Decision-making: Psychiatric Implications

As risk-reward decision-making enters into multiple aspects of everyday life, it is not surprising that individuals with impairments in brain regions involved in risk-reward decision-making would have difficulties in functioning successfully in real-life situations. Individuals with psychiatric disorders that are often characterized by immoral behaviors (e.g., substance abuse or dependence, antisocial personality disorder, pathological gambling) also frequently have problems in major areas of life functioning. Individuals with these disorders (e.g., cocaine dependence, other substance dependence or pathological gambling) have been found to perform more disadvantageously than healthy

control subjects on the Iowa Gambling Task (Petry, 2001b; Cavedini et al., 2002; Bechara, 2003), and amongst subjects with addictions, poor performance was associated with real-life measures of poor functioning; e.g., inability to hold a job (Bechara, 2003).

Other cognitive tasks have been used to assess risk-reward decision-making. For example, delay discounting tasks assess the extent to which individuals place value on smaller, immediate rewards as compared to larger, delayed ones. Based upon behavioral economic theories, the task assesses the extent to which one prefers specific amounts of money now or at a later time; e.g., $14 today or $25 in 19 days or $25 today or $30 in 80 days (Bickel et al., 1993; Bickel et al., 1999; Kirby et al., 1999). By using a range of time delays and amounts, one can generate discounting curves to examine the extent to which money loses value for individuals over time ("temporal discounting"). Individuals with pathological gambling, like those with drug dependence, tend to discount rewards rapidly; that is, immediate rewards have relatively greater saliency than do delayed ones in individuals with these disorders as compared to those without (Petry and Casarella, 1999; Petry, 2001a,b). Thus, understanding the biological mechanisms underlying reward processing and the selection of immediate as compared with delayed rewards has important implications for understanding, preventing and treating pathological gambling.

Biological Aspects of Reward Processing

Brain imaging techniques have been used to identify regions contributing to the selection of small, immediate rewards as compared to larger, delayed ones. In healthy volunteers, brain regions including the ventromedial prefrontal cortex and ventral striatum were found to activate following the selection of small immediate rewards

(McClure et al., 2004). Prior studies have identified neuronal connections between these brain regions that work together as components of the limbic system, and this neural circuit that underlies reward processing has been repeatedly implicated in addictive processes (Goldstein and Volkow, 2002; Chambers et al., 2003; Everitt and Robbins, 2005). This circuitry also was impacted in Phineas Gage following his accident, as regions of the ventromedial prefrontal cortex were presumably destroyed by the tamping rod (Damasio, 1994). In contrast to the brain regions activated following the selection of small immediate rewards, the selection of larger delayed rewards was associated with greater activation of prefrontal cortical regions that have been previously implicated in higher order cognitive executive functioning (McClure et al., 2004).

Independent research has investigated brain regions contributing to specific phases of the processing of small immediate rewards. Based on work performed in primates (Schultz, 2000), the monetary incentive delay task was designed to investigate reward processing in humans (Knutson et al., 2000). The task involves a visual cue that signifies the condition (e.g., win $1, lose $1, win $5, lose $5, win $0.20, lose $0.20, zero win/lose). Following the cue, a box appears on screen for a short period of time. Individuals are instructed to push a button while the box is on screen in order to win or avoid losing, respectively, the amount of money indicated for the condition. Shortly thereafter, participants learn of the outcome (whether or not they have won or avoided losing). In healthy adults, the anticipation of working for monetary reward was associated with activation of the ventral striatum whereas winning outcomes were associated with activation of the ventromedial prefrontal cortex (Knutson et al., 2001a,b; Knutson 2003). Together, these data suggest that the ventral striatum and ventromedial

prefrontal cortex each contribute to specific aspects of reward processing in healthy adults.

Neural Correlates of Reward Processing in Addiction

As individuals with pathological gambling and substance use disorders show behavioral differences in risk-reward decision-making, an understanding of how brain function in individuals with these disorders as compared to those without has important implications. Preliminary studies of adults with alcohol dependence as compared to those without have found relatively diminished activation of the ventral striatum during the anticipation of working for monetary reward in the monetary incentive delay task (Hommer, 2004). This finding extends to groups of individuals at high risk for alcoholism (for example, those with a positive family history of alcoholism (Hommer et al., 2004)) as well as groups with high rates of risk and addictive behaviors (for example, adolescents as compared with adults (Bjork et al., 2004)). Studies of cocaine dependent individuals have found disruptions in orbitofrontal and prefrontal circuits contributing to reward processing in control comparison subjects (Goldstein et al., 2007). Together, these findings indicate altered fronto-striatal brain function contributing to differences in reward processing in drug-addicted as compared with non-addicted individuals, and some of these functional brain differences extend to groups vulnerable to developing addictions.

Brain Imaging in Pathological Gambling: Ventromedial Prefrontal Cortex

Compared to other psychiatric disorders, relatively few brain imaging studies have been performed in subjects with pathological gambling. However, the studies that have been performed have implicated some of the same brain regions identified in studies of reward processing and drug addiction and implicated in the case of Phineas Gage. For example, in a functional magnetic resonance imaging (fMRI) study of gambling urges, subjects with pathological gambling as compared to those without showed relatively diminished activation of the ventromedial prefrontal cortex during the period of viewing the most robust gambling stimuli. This between-group difference was not observed during the control comparison conditions (happy or sad stimuli) (Potenza et al., 2003a). In a separate fMRI study of cognitive control using the Stroop Color-Word Interference Task, individuals with pathological gambling as compared to those without showed relatively diminished activation of the ventromedial prefrontal cortex following the presentation of incongruent stimuli (mismatched color-word pairs) (Potenza et al., 2003b). A third fMRI study of simulated gambling found that individuals with pathological gambling as compared to those without showed relatively diminished activation of the ventromedial prefrontal cortex in winning versus losing contrasts (Reuter et al., 2005). Amongst the group with pathological gambling, the degree of activation within the ventromedial prefrontal cortex correlated inversely with the severity of gambling problems. In other words, the more severe the gambling problem, the less the ventromedial prefrontal cortex became activated. Taken together, these three studies suggest an important role for the ventromedial prefrontal cortex in the pathophysiology of pathological gambling.

Brain Imaging in Pathological Gambling: Ventral Striatum

As described above, the ventral striatum makes important contributions to motivated behaviors and reward processing and has been implicated repeatedly in drug addiction (Knutson et al., 2001a,b; Chambers et al., 2003; Volkow and Li, 2004; Chambers et al., 2007). Individuals with pathological gambling have been found to show diminished activation of the ventral striatum during simulated gambling and activation of this brain region correlated inversely with gambling severity amongst the subjects with pathological gambling (Reuter et al., 2005). Preliminary data suggest that gambling urges in individuals with pathological gambling and cocaine cravings in individuals with cocaine dependence are similarly characterized by relatively diminished activation of the ventral striatum and orbitofrontal cortex (Potenza, 2007c). Further research is needed to investigate the extent to which brain activations related to other processes (e.g., reward processing) might be explained by functional differences in specific brain regions like the ventral striatum.

Neurochemical Contributions to Pathological Gambling

Although fMRI is a powerful technique for identifying functional contributions of brain regions to specific cognitive tasks, it does not allow for evaluation of the involvement of specific neurotransmitters in these processes. Other ligand-based imaging approaches (e.g., positron emission tomography or PET) permit such assessments but no ligand-based investigations involving subjects with pathological gambling have been published in peer-reviewed journals to date. Multiple neurotransmitter systems have been implicated in pathological gambling (Potenza and

Hollander, 2002; Brewer and Potenza, in press; Williams and Potenza, in press).

Dopamine has been hypothesized to contribute to rewarding and reinforcing behaviors,

serotonin to behavioral initiation and cessation, norepinephrine to arousal and excitement,

and opioids to pleasure and urges (Potenza and Hollander, 2002). Compared to control

subjects, individuals with pathological gambling have shown differences with respect to

each of these neurotransmitters.   These systems will be considered with respect to some

of the brain regions implicated in brain imaging studies of pathological gambling.

Serotonin in Pathological Gambling

        A role for the neurotransmitter serotonin in impulse control has been described for

several decades. Low levels of the serotonin metabolite 5-hydroxy-indole-acetic acid

have been found in the cerebrospinal fluid samples from multiple groups of individuals

characterized by impaired impulse control including those with alcoholism, impulsive

fire setting, or pathological gambling (Potenza and Hollander, 2002). Individuals

characterized by impaired impulse control also show different biochemical and

behavioral responses to serotonergic drugs (DeCaria et al., 1998). For example,

individuals displaying impulsive antisocial behaviors or those with alcohol dependence or

pathological gambling have reported a "high" or a "buzz" to the partial serotonin agonist

meta-chlorophenyl piperazine (mCPP) (DeCaria et al., 1998).   In contrast, healthy

control subjects do not report a euphorigenic response. Serotonergic drugs like mCPP

and fenfluramine have been examined in conjunction with brain imaging techniques in

individuals characterized by impaired impulse control, including those with alcohol

dependence and impulsive aggression. In response to these drugs, relatively diminished

activation or response within the ventromedial prefrontal cortex was observed in the group with impaired impulse control as compared to the control comparison group (Hommer et al., 1997; Siever et al., 1999; New et al., 2002). No such imaging study to date has examined the role of serotonin in ventromedial prefrontal cortical functioning in individuals with pathological gambling.

Dopamine in Pathological Gambling

The ventral striatum is a target region for dopamine neurotransmission within the mesolimbic pathway, and dopamine function within the ventral striatum contributes to reward-based learning in addiction (Chambers et al., 2003; Nestler, 2004; Volkow and Li, 2004). Several lines of evidence suggest a role for dopamine in pathological gambling, although its precise role requires further investigation. For example, decreased levels of dopamine and increased levels of dopamine metabolites (suggestive of higher dopamine turnover) were reported in the cerebrospinal fluid samples of individuals with pathological gambling (Bergh et al., 1997). However, dopaminergic differences did not persist when correcting for differences in flow rate of the fluid (Nordin and Eklundh, 1998; Nordin and Eklundh, 1999). Amphetamine, a drug with influences on dopaminergic and other biogenic aminergic systems, was found to cross-prime for gambling-related phenomena in individuals with pathological gambling, a finding suggestive of a pro-dopaminergic effect on gambling in the disorder (Zack and Poulos, 2004). A study from the same group found that haloperidol, a drug that blocks dopamine D2/D3 receptors, enhances the rewarding and priming effects of gambling in individuals with pathological gambling (Zack and Poulos, 2007). Among individuals with

Parkinson's disease (one that involves degeneration of dopamine systems), an association between dopamine agonist treatment and impulse control behaviors including excessive gambling has been reported (Voon et al., 2006a,b; Weintraub et al., 2006; Voon et al., 2007). However, other factors (e.g., early onset of Parkinson's disease) have also been associated with the emergence or worsening of impulse control behaviors in this population, making the precise nature of the involvement of dopamine systems unclear (Voon et al., 2006a,b; Weintraub and Potenza, 2006; Weintraub et al., 2006; Voon et al., 2007). As described above, ventral striatal function has been implicated in brain imaging studies of pathological gambling. However, no investigations to date have directly examined a possible role for ventral striatal dopamine dysfunction in pathological gambling.

Opioids in Pathological Gambling

Neurotransmitter systems and brain regions do not work in isolation but rather function in circuits in a dynamic fashion. Opioid systems influence dopamine function in the ventral striatum and a proposed mechanism of action for drugs that block opioid receptors is through indirect modulation of mesolimbic dopamine function (Grant et al., 2006; Williams and Potenza, in press). The opioid antagonist naltrexone is approved for the treatment of alcohol dependence and has shown efficacy in a placebo-controlled trial involving subjects with pathological gambling (Kim et al., 2001). Like in studies of alcohol use behaviors, the medication appeared particularly helpful for people with strong gambling urges at treatment onset (Kim et al., 2001). A placebo-controlled, multi-center trial of the opioid antagonist nalmefene demonstrated superiority of active drug over

placebo and provided further support for a role for opioid systems in pathological

gambling (Grant et al., 2006).   However, preliminary results of a subsequent trial of

nalmefene in pathological gambling did not generate positive findings (Biotie, 2007). A

similar variability has been observed in studies of alcohol dependence (Krystal et al.,

2001). Variability in study outcomes might be related to individual differences amongst

subjects. For example, commonly occurring variants of the gene encoding the mu-opioid

receptor have been associated with differential outcomes during treatment of alcohol

dependence with naltrexone (Oslin et al., 2003). The extent to which the mu-opioid

receptor gene variants or other specific biological factors might be related to treatment

outcome in pathological gambling warrants further investigation.

Genetics of Pathological Gambling

Technological advances have facilitated investigations into genetic factors

contributing to the development of psychiatric disorders. Molecular genetic

investigations have been performed in pathological gambling and have implicated genes

related to multiple neurotransmitter systems including dopamine and serotonin (Ibanez et

al., 2003; Williams and Potenza, in press). However, many of these studies have

significant methodological limitations (Ibanez et al., 2003) and more conclusive studies

await performance and/or publication. Large samples of twins allow for the estimation of

genetic and environmental contributions to mental health disorders like pathological

gambling (Shah et al., 2005).   Like with other psychiatric conditions, data indicate that

there exist substantial contributions to pathological gambling (Eisen et al., 1998), with

genetic contributions to the disorder accounting for approximately two-thirds of the

variance and environmental factors for about one-third (Potenza et al., 2005). Genetic

factors contributing to pathological gambling have been found to overlap with those for

alcohol dependence (Slutske et al., 2000) and those for antisocial behaviors (Slutske et

al., 2001), suggesting that common genetic contributions exist between excessive forms

of gambling and other behaviors that have been described as immoral. These studies also

identified overlaps in the environmental contributions suggesting that both heredity and

life experience factors make significant contributions to these disorders and their co-

occurrences.

Genetic and environmental factors have been shown to interact significantly in the

development of psychiatric disorders. For example, individuals with a specific variant of

the serotonin transporter allele who are exposed to early life stress are significantly more

likely to experience depression than are individuals with the same allele not exposed to

such stressors or individuals with a different variant irrespective of stress exposure (Caspi

et al., 2003). Although stress exposure has been associated with pathological gambling

(particularly among women) (Petry et al., 2005), the interaction with specific genetic

factors has not been reported. Commonly occurring genetic variants also can

substantially influence patterns of brain activation, including within regions related to

stress-responsiveness, emotional regulation and cognition (Egan et al., 2001; Hariri et al.,

2002). The extent to which these and other genetic variants influence moral behaviors in

psychiatric and non-psychiatric groups warrants further examination.

The identification of genetic contributions to disorders or behaviors that can be

characterized as immoral suggests that certain individuals are born with a greater

likelihood than are others for behaving in an immoral fashion. The identification of

environmental contributions to these disorders suggests that specific life events can influence the development of these disorders and enactment of these behaviors, providing hope for prevention and treatment efforts.

Neurobiology of Ethics and Morality

Technological advances in imaging and genetics have provided exciting opportunities to investigate not only gambling, but also other behaviors and disorders with moral or ethical implications (Friedrich 2005). Results from these studies have are relevant to multiple disciplines including philosophy, sociology, ethics, religion the law among others, and investigators with expertise in different domains (neuroscience, psychology, evolutionary biology, anthropology, etc.) are contributing to an emerging field of cognitive neuroscience of human behaviors (Adolphs, 2003; Moll et al., 2005a).

Moral reasoning and behaviors encompass a broad range of complex behaviors influenced by cognitive, social, and emotional factors (Greene et al., 2004; Moll et al., 2005a). Although reasoning and cognitive processing were emphasized for decades, more recent work has examined intuitive or emotional and social influences on moral processes (Greene and Haidt, 2002; Greene et al., 2004). Within the emotional domain, "social" emotions such as guilt, embarrassment, pride and jealousy are particularly relevant to moral reasoning and behaviors (Adolphs, 2003). Moral judgments have been categorized in fashions that reflect differential contribution from cognitive, social and emotional domains. For example, one classification defines personal and impersonal moral judgments in which the former are guided to a relatively greater extent by social and emotional contributions and the latter to a relatively greater extent by cognitive

contributions (Greene et al., 2004). However, this and similar models have been criticized in that they may not fully account for cultural influences on moral reasoning and decision-making (Moll et al., 2005a).   Nonetheless, existing studies suggest that moral cognitions and behaviors involve a broad range of brain regions involved in cognitive and emotion processes in a social-context-dependent fashion, with different types of moral dilemmas activating preferentially different aspects of these neural circuits.

Consistent with this hypothesis, existing data differentially implicate specific brain regions in negotiating different moral processes. Amongst the brain regions most typically implicated in imaging paradigms probing moral cognition and behavior include cortical regions (e.g., ventromedial prefrontal cortex, lateral orbitofrontal cortex, anterior prefrontal cortex, dorsolateral prefrontal cortex, anterior temporal cortex, and superior temporal sulcus) and subcortical regions (amygdala, ventromedial hypothalamus, septal area and nuclei, and basal forebrain, particularly the ventral striatum/pallidum and extended amygdala) (Moll et al., 2005a). These regions include those described above in the cases of Phineas Gage and pathological gambling, and reflect the complexity of the networks underlying moral reasoning and behaviors. Moral reasoning and behaviors seem differentially determined in part through developmental influences on these brain regions. For example, while damage to the ventromedial prefrontal cortex in adulthood has been associated with deficits in moral behaviors but not moral reasoning (Elsinger and Damasio, 1993), damage at an early age has been associated with impairments in both areas (Anderson et al., 1999). Individuals with damage to this brain region also show deficiencies in pride, embarrassment and regret (Beer et al., 2003; Camille et al.,

2004). Ventromedial prefrontal and orbitofrontal cortex and amygdala are considered important contributors to social response reversal theory (commission of immoral behaviors related to difficulties in learning following negative outcomes), violent inhibition mechanism (deficiency in controlling aggressive behaviors) and somatic marker hypothesis (integration of emotional and cognitive processing in decision-making) models of moral behaviors (Moll et al., 2005a). However, these models do not necessarily account for specific prefrontal cortical regions in moral reasoning and behaviors (Moll et al., 2005a). Brain regions important for conflict monitoring and cognitive control (for example, the lateral prefrontal cortex and dorsal anterior cingulate cortex (Botvinick et al., 1999; Botvinick et al., 2001)) also contribute to moral processing, with hypotheses positing that these cortically regions exhibit control over emotional ones in circumstances of utilitarian or impersonal moral dilemmas and vice-versa in the case of personal moral dilemmas (Moll et al., 2005a).

In contrast to theories that hypothesize a hierarchical relationship between emotions and cognition, several recent theories hypothesize an integrated model across these and other domains. For example, the event-feature-emotion complex framework posits that social, motivational, emotional, and contextual information is bound together (Moll et al., 2005a). This model hypothesizes that information from these domains are processed and integrated with key brain regions more centrally involved in specific aspects. Specifically, structured event knowledge is supplied by prefrontal cortical subregions, social perceptual or functional features in temporal cortex, and motivational and basic emotional states in limbic and paralimbic regions (Moll et al., 2005a). Consistent with this model, moral emotional states like compassion (Moll et al., 2005a),

embarrassment (Takahashi et al., 2004), indignation (Moll et al., 2005b) and guilt (Shin et al., 2000; Takahashi et al., 2004) have been associated with activations of these regions. However, this and competing models require further evaluation as to how they relate to moral judgment and behaviors in clinical and community samples.

Clinical samples may provide insight into aspects of social cognition and moral processing. For example, clinical groups characterized by antisocial behavior (e.g., sociopathy (Blair, 2003)) or excessive prosocial engagement (e.g., Williams Syndrome (St. George and Bellugi, 2000)) show abnormalities in the amygdala. Violent behaviors have been associated with orbitofrontal cortical abnormalities in antisocial personality disorder, although other brain regions (e.g., sensorimotor cortex) have also been implicated in this and other patient groups (Narayan et al., 2007). Damage to the bilateral temporal cortices or amygdala has been associated with social and appetitive disturbances (hypersexuality, placidity, and hyperorality and pica) (Hayman et al., 1998). The extent to which social and moral processing differs in individuals with pathological gambling as compared to those without warrants further investigation. Given that moral perceptions influence brain activations within reward processing regions (including striatum) in healthy subjects, it will be important to evaluate these processes as related to gambling behaviors.

Conclusions and Future Directions

Technical advances in genetics and brain imaging are providing important insight into brain processes related to moral reasoning and behavior. These advances in neuroscience research methodologies are also generating a better understanding of brain

function underlying mental health and illness. Future research should examine more closely the relationships between these domains. The acquisition of knowledge about individual brain function with respect to moral and medical states raises questions about privacy and ethics (Friedrich, 2005). Although how best to use this information in various settings (e.g., legal, medical, and ethical venues) is currently a topic of discourse (Leshner, 2003; Friedrich, 2005; Buller, 2006; Eastman and Campbell, 2006), the knowledge should help further discussion about the roots of moral and immoral thoughts and behaviors. As applied to human health and disease, these advances offer hope to advance prevention and treatment strategies, diminish individual suffering, and promote societal well-being.

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