

Neurobiology of Wisdom

A Literature Overview

Thomas W. Meeks, MD; Dilip V. Jeste, MD

Context: Wisdom is a unique psychological trait noted since antiquity, long discussed in humanities disciplines, recently operationalized by psychology and sociology researchers, but largely unexamined in psychiatry or biology.

Objective: To discuss recent neurobiological studies related to subcomponents of wisdom identified from several published definitions/descriptions of wisdom by clinical investigators in the field, ie, prosocial attitudes/behaviors, social decision making/pragmatic knowledge of life, emotional homeostasis, reflection/self-understanding, value relativism/tolerance, and acknowledgment of and dealing effectively with uncertainty.

Data Sources: Literature focusing primarily on neuroimaging/brain localization and secondarily on neurotransmitters, including their genetic determinants.

Study Selection: Studies involving functional neuroimaging or neurotransmitter functioning, examining human (rather than animal) subjects, and identified via a PubMed search using keywords from any of the 6 proposed subcomponents of wisdom were included.

Data Extraction: Studies were reviewed by both of us, and data considered to be potentially relevant to the neurobiology of wisdom were extracted.

Data Synthesis: Functional neuroimaging permits exploration of neural correlates of complex psychological attributes such as those proposed to comprise wisdom. The prefrontal cortex figures prominently in several wisdom subcomponents (eg, emotional regulation, decision making, value relativism), primarily via top-down regulation of limbic and striatal regions. The lateral prefrontal cortex facilitates calculated, reason-based decision making, whereas the medial prefrontal cortex is implicated in emotional valence and prosocial attitudes/behaviors. Reward neurocircuitry (ventral striatum, nucleus accumbens) also appears important for promoting prosocial attitudes/behaviors. Monoaminergic activity (especially dopaminergic and serotonergic), influenced by several genetic polymorphisms, is critical to certain subcomponents of wisdom such as emotional regulation (including impulse control), decision making, and prosocial behaviors.

Conclusions: We have proposed a speculative model of the neurobiology of wisdom involving frontostriatal and frontolimbic circuits and monoaminergic pathways. Wisdom may involve optimal balance between functions of phylogenetically more primitive brain regions (limbic system) and newer ones (prefrontal cortex). Limitations of the putative model are stressed. It is hoped that this review will stimulate further research in characterization, assessment, neurobiology, and interventions related to wisdom.

Arch Gen Psychiatry. 2009;66(4):355-365

Of all the pursuits open to men, the search for wisdom is most perfect, more sublime, more profitable, and more full of joy.

Thomas Aquinas (~1260)¹

W

ISDOM, A UNIQUE HUMAN attribute rich in history dating back to the dawn of civilization, is a newcomer to the world of empirical research. For centuries, wisdom was the sole province of religion and philosophy.² A standard philosophical (in Greek, *philosophia*=lover of wisdom) definition of wisdom pertains to judicious application of knowledge,³ and most religions have considered it a virtue. Wisdom is thought to be

a complex construct, with several subcomponents. While the relative emphasis on specific subcomponents has varied across cultures and periods, there have been more similarities than differences among different postulated concepts of wisdom. While classic Greek writings on wisdom focused on rationality, early Indian and Chinese thinkers stressed emotional balance.^{4,5} Yet, these conceptualizations of wisdom shared several common features, such as thoughtful decision making, compassion, altruism, and insight. Excellent accounts of the history of the concept of wisdom are available.⁵⁻⁸

In the 19th century, Gall, who popularized the pseudoscience of phrenology,

Author Affiliations:

Department of Psychiatry and Sam and Rose Stein Institute for Research on Aging, University of California, San Diego (Drs Meeks and Jeste); and VA San Diego Healthcare System (Dr Jeste).

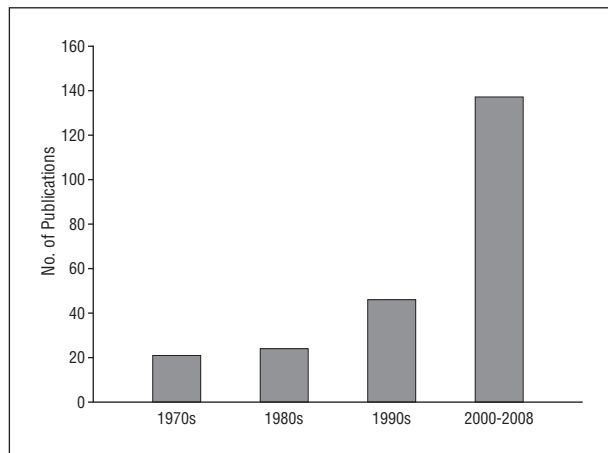


Figure 1. The numbers of publications from a PubMed search from January 1970 through April 2008 that addressed wisdom as a psychological or cognitive construct.

included among its 27 mental functions “comparative sagacity,” at times called wisdom, and assigned it to prefrontal regions.⁹ It was, however, only a few decades ago that sociology, psychology, and gerontology began considering wisdom as a subject worthy of discussion, albeit a controversial one. Erikson¹⁰ suggested that the last stage of his 8-stage theory of psychosocial development, from about age 65 years to death, centered on conflict resolution between ego integrity and despair, with successful resolution culminating in wisdom. In the 1970s, Baltes et al,¹¹ Clayton,¹² and others¹³ initiated empirical research in this area. Although the initial western theories of wisdom focused on cognitive abilities, Ardeli¹⁴ and others drew attention to the importance of emotional self-regulation. The evolving modern conceptualization of wisdom bears remarkable similarities to some of the oldest concepts of wisdom postulated in the Bhagavad Gita, an Indian religious text written several centuries BC.⁴

Recent years have witnessed paradigm shifts in medicine, moving the spotlight from disease to health, from treatment to prevention, and from risk factors to protective factors. Similarly, several positive psychological constructs have attracted growing academic interest as psychiatry has begun to appreciate the need for studying protective psychological traits such as resilience, instead of a singular focus on psychopathology.¹⁵⁻¹⁸ A few mental health researchers have noted the value of examining wisdom.^{19,20} There are now several scales for assessing wisdom, with variable psychometric properties.^{14,21,22} Overall, literature on wisdom continues to expand. As **Figure 1** shows, the number of articles on the construct of wisdom found in a PubMed database search using the keyword “wisdom” has increased 7-fold from the 1970s through 2008. The topic of wisdom is also being discussed in prominent lay media,²³ clinical medicine,²⁴⁻²⁶ and learning theories.²⁷

The following overview is based on our interpretation of the literature on wisdom. It clearly would be unwise of us to claim this interpretation as a definitive model. Our goal is to stimulate discourse and research in an important but neglected area of investigation. Subsequent empirical research may lead to substantial

- I. Prosocial attitudes and behaviors
 - “Achievement of a common [social] good” (Sternberg)¹³
 - “Implicit idea that wisdom serves a common good” (Baltes et al)¹¹
 - Factor analysis yielded “altruism” as a dimension of wisdom (Brown and Greene)²⁹
 - Affective wisdom includes “positive emotion and behaviors toward others, and absence of indifferent or negative emotions toward others” (Ardelt)¹⁴
 - One of 5 dimensions of wisdom is warmth (Jason et al)²²
- II. Social decision making/pragmatic knowledge of life
 - Two basic criteria: (1) rich factual knowledge regarding human nature and life course and (2) rich procedural knowledge regarding ways of dealing with life’s problems (Baltes et al)¹¹
 - The tacit nature of knowledge implies more than knowing but also knowing when, where, how, and why to apply knowledge (Sternberg)¹³
 - “Practical knowledge” as a dimension of wisdom (Meacham)²¹
 - Practical wisdom is “good interpersonal skills and understanding, expeditious use of information, and expertise in advice giving” (Wink and Helson)²¹
 - Three dimensions of wisdom include judgment, life knowledge, and life skills (Brown and Greene)²⁹
- III. Emotional homeostasis
 - Emotional stability despite uncertainty as a component (Brugman)²¹
 - Affective wisdom includes “absence of indifferent or negative emotions toward others, and remaining positive in the face of adversity” (Ardelt)¹⁴
 - One dimension of wisdom: emotional management (Brown and Greene)²⁹
- IV. Reflection/self-understanding
 - Reflective abilities are a key component of wisdom (Meacham)²¹
 - Reflective judgment an important part of wisdom (Kitchener)²¹
 - Transcendental wisdom comprises interest in self-understanding (Wink and Helson)²¹
 - Reflective wisdom is 1 of 3 key dimensions of overall wisdom (Ardelt)¹⁴
 - Self-knowledge identified as a dimension of wisdom (Brown and Greene)²⁹
- V. Value relativism/tolerance
 - Value relativism and tolerance 1 of 3 meta-criteria for wisdom (Baltes et al)¹¹
 - Value relativism seen as a component of wisdom (Meacham)²¹
 - As part of reflective wisdom: “ability and willingness to examine phenomena from multiple perspectives; absence of projections” (Ardelt)¹⁴
 - “Tolerant and understanding” part of descriptors of Practical Wisdom Scale (Wink and Helson)²¹
- VI. Acknowledgment of and dealing effectively with uncertainty and ambiguity
 - “Handling of uncertainty, including the limits of knowledge” (Baltes et al)¹¹
 - Comprehension of/dealing with uncertainty (Meacham)²¹
 - “3 key components: (1) Meta-cognition (acknowledging uncertainty and ability for dialectical thinking); (2) Personality/affect (emotional stability despite uncertainty and openness to new experience); (3) Behavior (ability to act in the face of uncertainty)” (Brugman)²¹
 - “Cognitive wisdom includes awareness of life’s inherent uncertainty yet ability to make decisions in spite of this” (Ardelt)¹⁴

Figure 2. Commonly proposed subcomponents of wisdom.

revision or even repudiation of the putative model we describe herein.

Although there is no consensual definition of wisdom, we believe that wisdom is a unique psychological construct, not just a collection of desirable traits with a convenient unifying label. Wisdom may be viewed as a trait comprising several subcomponents. We searched the published literature on wisdom to identify definitions and found 10 major definitions or descriptions.^{11,13,14,21,22,28,29} Despite some variations in terms, we (T.W.M. and D.V.J.) agreed that the following 6 subcomponents of wisdom were included in at least 3 of these definitions: (1) prosocial attitudes/behaviors, (2) social decision making/pragmatic knowledge of life, (3) emotional homeostasis, (4) reflection/self-understanding, (5) value relativism/tolerance, and (6) acknowledgment of and dealing effectively with uncertainty/ambiguity. **Figure 2** presents these subcomponents along with the researchers who included them as a part of their descriptions of wisdom. A few authors have emphasized other domains of wisdom, such as religiosity, intuition, or epistemology,

but these were not included in at least 3 of the earlier-mentioned definitions.

We view wisdom as a trait distributed in the general population along a continuum rather than as a rare attribute³⁰ restricted to iconic individuals like Mother Teresa, Mahatma Gandhi, and Nelson Mandela.⁵ Although it is somewhat stable as a trait within an individual, it is also shaped, to a significant extent, by experience and learning. There are inevitable overlaps between wisdom and other constructs, such as resilience and social cognition, that share certain psychological attributes, including emotional regulation and social decision making. Nonetheless, the construct of wisdom is distinct, as it includes several domains not essential for these other constructs.

Wisdom is considered an important contributor to successful personal and social functioning.^{19,31} Understanding the neurobiology of wisdom may have considerable clinical significance. For example, knowledge of the underlying mechanisms could potentially lead to development of preventive, therapeutic, and rehabilitative interventions for enhancing wisdom, including those designed for persons with relevant neuropsychiatric disorders (eg, frontotemporal dementia). Yet, neurobiology researchers have stayed away from investigating wisdom, in part, because of difficulties in defining the phenotype. Indeed, we found no studies in a PubMed database search using the keyword “wisdom” in combination with the terms *neurobiology*, *neuroimaging*, and *neurotransmitters*.

We, therefore, decided to examine the literature on the neurobiology of each of the earlier-mentioned 6 subcomponents of wisdom, focusing on their putative neuroanatomical localization determined primarily by functional neuroimaging with a secondary focus on neurotransmitter functions (including their genetic determinants). Studies involving functional neuroimaging or neurotransmitter functioning, examining human (rather than animal) subjects, and identified via a PubMed search using keywords from any of the 6 proposed subcomponents of wisdom were included. These studies were reviewed by both of us (T.W.M. and D.V.J.), and data considered to be potentially relevant to the neurobiology of wisdom were extracted. Possible intermediate phenotypes (the more easily measured emotional and cognitive functions relevant to subcomponents of wisdom) may be localized to certain brain regions. As will be summarized later, the neurobiological substrates of different subcomponents of wisdom seem to include several common regions, such as the prefrontal cortex (PFC), especially dorsolateral PFC (DLPFC), orbitofrontal cortex (OFC), medial PFC (MPFC), and anterior cingulate, and certain subcortical structures (mainly amygdala and striatum) and are strongly influenced by monoaminergic pathways.

NEUROBIOLOGY OF SUBCOMPONENTS OF WISDOM

Prosocial Attitudes and Behaviors

One of the most consistent subcomponents of wisdom, from both ancient and modern literature, is the promotion of common good and rising above self-interests, ie,

exhibiting prosocial attitudes and behaviors, such as empathy, social cooperation, and altruism.⁶ Thus, sociopaths, who may exhibit exquisite social cognition and emotional regulation that actually facilitate their selfish motives, would not be considered wise.

Brain Localization via Neuroimaging. *Empathy.* Empathy facilitates other prosocial behaviors, including altruism.^{32,33} Mirror neurons, originally discovered in primates³⁴ and later demonstrated in the human inferior frontal gyrus using neurophysiological methods and functional neuroimaging, may be primitive neurobiological substrates for empathy. In the PFC, mirror neurons fire in the same pattern while a person is performing an action and while watching someone else perform the same action, suggesting their role in appreciating nonverbal communication.³⁵ Persons with greater unconscious somatic mimicry have higher ratings of self-reported altruism.³⁶ When children observe and imitate facial expressions, mirror neurons are activated, and this activity correlates with empathy scores.³⁷ Human empathy is obviously more complex than somatic mimicry. It requires consciously taking the perspective of another person, which is related to the “theory of mind,” developed by Perner and Lang³⁸ as a model of how a person understands other people’s mental states and emotions. Neuroimaging research in “theory of mind” tasks has consistently shown MPFC and posterior superior temporal sulcus activation.³⁹⁻⁴² The MPFC appears involved in “mentalizing” or conceiving of the inner world of others, whereas posterior superior temporal sulcus activation occurs in response to visual stimuli relevant to internal mental states (eg, body gestures, facial expressions).

A functional magnetic resonance imaging (fMRI) study implicated MPFC in perception of shared emotional experiences.⁴³ A meta-analysis of 80 studies concluded that MPFC had a prominent role in empathy.⁴⁴ Individuals activate MPFC while making empathic social judgments,⁴⁵ and ventromedial PFC (vmPFC) lesions predict empathic deficits.⁴⁶ Also critical to empathy is an awareness of self- vs other differentiation to avoid mere emotional contagion. An fMRI study indicated that the superior temporal gyrus and inferior parietal lobe might be critical for self- vs other differentiation of emotions.⁴⁷

Social Cooperation. Social cooperation (vs competition) likewise appears related to prosocial motives⁴⁸ and has received attention in neuroimaging research, using a variety of tasks (eg, trust/reciprocity games including the “Prisoner’s Dilemma”). Functional MRI studies have demonstrated that social cooperation activates MPFC and nucleus accumbens/ventral striatum, the latter being regions involved in central reward circuitry.⁴⁹⁻⁵¹ Likewise, “altruistic punishment” (punishment of violators of social norms at cost to oneself) activates reward neurocircuitry.⁵² In contrast, social competition either decreases activity in areas activated by cooperation⁵³ or activates other regions such as DLPFC.⁵⁰ In an fMRI study, persons with high sociopathy ratings showed (relative to comparison subjects) decreased amygdala response while being uncooperative during a social cooperation task and less OFC activity while cooperating, suggesting a lack of aversive

emotions while violating social norms and a lack of positive emotions while exhibiting social cooperation.⁵⁴

Altruism. Altruism overlaps with cooperation, although altruism is notable for the potential harm or “decreased fitness” the altruistic person risks to help others.⁵⁵ Harbaugh and colleagues⁵⁶ demonstrated that the idea of voluntarily giving money compared with that of paying taxes (still perceived as a needed social good) caused increased activation in reward circuitry (caudate and nucleus accumbens). Similarly, Moll et al⁵⁷ reported that both receiving monetary rewards and deciding to donate money activated ventral and dorsal striatum. This somewhat paradoxically suggests that the neural substrate of altruism may be akin to that of more instinctual self-pleasures.

Neurotransmitters and Genetics. Several genetic studies have reported that the heritability of prosocial behaviors, including altruism, is 50% to 60%.⁵⁸⁻⁶⁰ Moreover, research indicates involvement of monoamines and certain neuropeptides. This evidence is summarized in **Table 1**, with findings most notable for the roles of dopamine, serotonin, and the hypothalamic neuropeptides vasopressin and oxytocin in prosocial attitudes/behaviors.

Summary. **Table 2** summarizes the role of various brain regions in promoting prosocial behavior (along with the other wisdom subcomponents described later). Prosocial behaviors are facilitated by empathy (rooted in mirror neurons and MPFC) and include social cooperation and altruism (tied to reward neurocircuitry and variations in monoaminergic/hypothalamic peptide functioning).

Social Decision Making/Pragmatic Knowledge of Life

The pragmatic knowledge and skills included in concepts of wisdom have not been directly studied biologically. Implicit in the descriptions of Baltes et al⁸⁸ of “rich factual knowledge regarding human nature” and “knowledge regarding ways of dealing with life’s problems” is the notion of dealing effectively with the constant complex social situations with which humans are confronted. Later we describe several studies related to social cognition and social (including moral) decision making, relevant to this dimension of wisdom. While this overlaps somewhat with the earlier-mentioned concept of prosocial behaviors, there appear to be neurobiological differences between experiencing shared emotions/goals and understanding others’ emotions and behaviors. After recognizing and understanding others’ emotions and motivations, as “theory of mind” facilitates, one may then use this information to make (or not make) “wise” social decisions.

Brain Localization via Neuroimaging. *Decision Making.* Ernst and Paulus⁸⁹ reviewed the neurobiological circuits implicated in decision making, emphasizing differences in regions involved depending on which stage of decision making was being tested—forming a preference, executing an action, or evaluating an outcome. The first and last steps appeared to involve limbic and PFC regions, whereas executing an action was tied to striatal function.⁸⁹ Montague and Berns⁹⁰ stress that underlying each decision are both

a representation of choices and a short-term (and sometimes distal) evaluation of the consequences of those choices. One aspect of wisdom is balancing choices based on immediate reward vs long-term consequences; as Osbeck and Robinson described, “contemplation of variable things is the function of practical wisdom.”^{91(p68)} This apparently involves a “top-down” interaction between the lateral PFC and emotion- and reward-based circuitry in limbic cortex and striatum, akin to regulation of impulsivity, discussed later. Consistent with this notion, McClure and colleagues⁹² demonstrated that choosing immediate rewards activated limbic and paralimbic cortices, whereas choosing delayed rewards activated DLPFC and parietal regions. However, another report presented contradictory results—increased DLPFC activity in persons prone to immediate reward-based decisions and increased OFC activity with delayed reward-based decisions.⁹³ Whether differences in rewards (money⁹² vs sugary drinks⁹³) were responsible for discrepant findings in these investigations is unclear. Supporting this latter study, OFC lesions have been reported to increase immediate reward bias and impulsivity.⁹⁴ In an investigation comparing decision making of adolescents and adults, increased risk-prone decision making was associated with less activity in ventrolateral PFC, OFC, and dorsal anterior cingulate cortex (ACC).⁹⁵ Despite some conflicting results, both OFC and lateral PFC likely play roles in facilitating decisions favoring delayed gratification over immediate reward.

Moral Decision Making. Moral decision-making tasks have been investigated using fMRI. One prerequisite for moral decision making is moral sensitivity, ie, the ability to recognize a moral dilemma. Moral sensitivity is correlated with activity in MPFC, posterior cingulate cortex (PCC), and posterior superior temporal sulcus.⁹⁶ Implicit emotion-based moral attitudes have been linked to amygdala and vmPFC activity.⁹⁷ Greene et al⁹⁸ also showed increased MPFC, PCC, and angular gyrus activation in “personal” vs “impersonal” moral reasoning tasks. In contrast, impersonal moral decision-making tasks preferentially activated lateral frontoparietal regions. Consistent with these findings, another study of “simple ethical decisions” (ie, not involving ambiguity, bodily harm, or violence) showed activated temporal and lateral PFC regions.⁹⁹ The role of PCC may, however, be more related to processing self-relevant emotional stimuli (as opposed to decision making per se), as another report showed increased PCC activity when subjects were presented with a moral dilemma and when they simply passively viewed the dilemma’s outcome.¹⁰⁰ Greene et al¹⁰¹ examined another angle of moral decision making by comparing neural activity in personal moral decisions vs utilitarian moral judgments, ie, those requiring possible violation of personal moral judgments and emotional self-interests for the sake of common social good (eg, actively sacrificing one person to save the lives of several others). These conflictual, utilitarian-based moral decisions activated ACC (involved in conflict detection) and DLPFC, likely recruited to use more “calculated and rational” thought processes to overcome automatic emotional responses. Consistent with this notion, persons with vmPFC damage were found to have an increased tendency for utilitarian moral decisions.¹⁰²

Table 1. Neurotransmitter Variants Associated With 2 Proposed Subcomponents of Wisdom: Prosocial Attitudes/Behaviors and Emotional Homeostasis

Wisdom Subcomponent	Neurotransmitter	Findings
Prosocial attitudes/behaviors	Dopamine	DRD ₄ and DRD ₅ polymorphisms associated with self-reported selflessness ⁶¹ ; striatal DRD ₂ receptor binding potential correlated with increased socially desirable responses ⁶²
	Serotonin	MAO-A polymorphisms associated with antisocial personality features ⁶³ ; decreased social cooperation in the Prisoner's Dilemma game (testing social cooperation) following dietary tryptophan depletion ⁶⁴
	Vasopressin	Strongly related to affiliative behavior in small mammals called voles; longer repeats in the RS3 promoter region of the <i>AVPR1a</i> gene in humans were associated with more altruistic actions in an in vivo game, higher self-reported altruism, and higher levels of postmortem <i>AVPR1a</i> messenger RNA ⁶⁵
Emotional homeostasis (including low impulsivity)	Oxytocin	Implicated in social cognition and social affiliation, particularly in the context of autism ⁶⁶
	Dopamine	DRD4, DAT, and COMT polymorphisms linked to risk for ADHD and/or measures of impulsivity ⁶⁷⁻⁶⁹ ; COMT Met/Met homozygosity associated with increased amygdala, hippocampus, and PFC activity in response to emotionally provocative stimuli and also with altered connectivity between ventrolateral PFC/OFC and amygdala/hippocampus ⁷⁰
	Serotonin	Polymorphism in the 5HT _{2A} receptor gene associated with variations in impulsivity scores as measured by go/no-go tasks ⁷¹ ; decreased availability of the serotonin transporter in anterior cingulate in persons with impulsive aggression vs comparison subjects ⁷² ; polymorphisms in MAO-A linked to impulsivity, including higher scores of impulsivity on go/no-go tasks, altered response of ventrolateral PFC during tasks assessing impulsivity, decreased OFC volume, and altered OFC-amygdala connectivity associated with elevated degrees of impulsivity ^{73,74} ; the (s) allele of 5HTT promoter region associated with decreased production of 5HTT and increased amygdala activity in response to emotional (vs neutral) stimuli ⁷⁵⁻⁷⁸ ; 5HTT (s) allele associated with decreased gray matter volume in subgenual ACC and amygdala and decreased functional connectivity between ACC and amygdala (implying impaired "top-down" emotional homeostasis) ⁷⁹ ; 5HTT (s) allele also associated with decreased 5HT _{1A} receptor binding (which may disrupt autoreceptor negative feedback loops), twice the risk of developing depression (vs (l)/(l) homozygotes) after stressful life events and increased baseline amygdala and hippocampus activity that correlated with severity of life stressors ⁸⁰⁻⁸² ; (T) allele of TPH-2, the rate-limiting enzyme of serotonin synthesis, associated with cluster B and C personality traits (eg, emotional dysregulation and interpersonal anxiety), enhanced amygdala response to emotional stimuli, and increased neuronal activity in event-related potentials in response to viewing emotional stimuli, with this latter result showing an additive effect of TPH-2 (T) allele and 5HTT (s) allele ⁸³⁻⁸⁵
	Norepinephrine	Polymorphism in α_2 -adrenergic receptor gene associated with elevated sympathetic and adrenomedullary responses to induced stress ⁸⁶ ; NPY, coreleased with norepinephrine, served to dampen further norepinephrine release and allow equilibration of the sympathetic response, and higher plasma levels of NPY facilitated better stress-associated performance ⁸⁷

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; AVPR, vasopressin receptor; COMT, catechol *O*-methyltransferase; DAT, dopamine transporter; DRD, dopamine receptor; MAO-A, monoamine oxidase inhibitor type A; NPY, neuropeptide Y; OFC, orbitofrontal cortex; PFC, prefrontal cortex; TPH, tryptophan hydroxylase; 5HT, serotonin; 5HTT, serotonin transporter.

Neurotransmitters and Genetics. Limited evidence indicates that dopamine and serotonin play roles in normal and abnormal social cognition; dopamine, in particular, influences reward bias in general decision making. Based largely on results from studies of autism and schizophrenia, 2 disorders with notably impaired social cognition,¹⁰³ one review outlined how both serotonin and dopamine may play important roles in social cognition, including the ability to mentalize, associated with the "theory of mind."¹⁰⁴

Summary. A number of brain regions are involved in social (including moral) decision making, especially DLPFC, vmPFC, ACC, and amygdala.

Emotional Homeostasis

Increasingly, wisdom researchers speak of integration of affective control and cognitive processes as being crucial to wisdom.¹⁴ Partly underlying emotional regulation is impulse control, which, as discussed earlier, is also relevant to decision making. While these 2 wisdom subcomponents share a substrate of impulse control, there are likely important differences in affective vs cognitive impulsivity. The purported role of emotional regulation

in wisdom has centered on inhibiting prolonged negative emotions. Yet, disinhibition of positive emotions, such as happiness, love, and gratitude, which may involve insula and spindle cells, deserves additional research.¹⁰⁵

Brain Localization via Neuroimaging. Impulse Control. Neuroimaging studies of impulse control have consistently implicated dorsal ACC and lateral PFC/inferior frontal gyrus.¹⁰⁶ Dorsal ACC appears to recognize a conflict between one's instinctual emotional response and a more reasonable overall social goal, whereas lateral PFC may maintain the overarching, more reasonable social goal in working memory and inhibit an inappropriate response. Behavioral inhibition as a specific component of impulse control is often tested with "go/no-go" tasks, designed to assess inhibition of activated or prepotent responses, eg, being asked to tap after hearing 1 tap but do nothing after hearing 2 taps.¹⁰⁷ Typically, inferior frontal gyrus activates in "no-go" responses (ie, those that require behavioral inhibition).¹⁰⁸

Reappraisal of Emotions. Reappraisal of emotions is a higher-order cognitive task involved in emotional homeostasis. Reframing negative emotional experiences as less aversive may involve recruitment of PFC regions (lateral, medial, and orbitofrontal) to dampen amygdala ac-

Table 2. Putative Neuroanatomical Localization of Cognitive or Emotional Tasks Relevant to Wisdom

Neuroanatomical Location	Associated Cognitive/Emotional Tasks	Putative Subcomponents of Wisdom Served
Anterior cingulate cortex	Conflict detection	Social decision making/pragmatic life knowledge; value relativism/tolerance
Posterior cingulate cortex	Moral sensitivity	Prosocial attitudes/behaviors
Superior temporal sulcus	Processing self-relevant stimuli	Reflection/self-understanding
	Self-other differentiation	Prosocial attitudes/behaviors
Lateral/dorsolateral prefrontal cortex	Socially relevant stimuli	Prosocial attitudes/behaviors
	Moral sensitivity	Prosocial attitudes/behaviors
	Top-down control of emotions/impulses	Social decision making/pragmatic life knowledge; emotional homeostasis; value relativism/tolerance
Medial/ventromedial prefrontal cortex	Effortful reasoning/executive functioning	Social decision making/pragmatic life knowledge
	Processing ambiguity	Acknowledgment of and dealing effectively with ambiguity
	Empathy/social bonds	Prosocial attitudes/behaviors
	Personal morality	Prosocial attitudes/behaviors
Orbitofrontal cortex	Self-reflection	Reflection/self-understanding
	Affectively charged decision making	Emotional homeostasis
	Inhibition of impulsivity	Social decision making/pragmatic life knowledge; emotional homeostasis
Amygdala	Encoding affective value of stimuli and reward expectation	Social decision making/pragmatic life knowledge; emotional homeostasis
	Emotional decisions	Emotional homeostasis
Nucleus accumbens/striatum	Aversive emotional reactivity	Emotional homeostasis
	Reward valence	Prosocial attitudes/behaviors; social decision making/pragmatic life knowledge
	Immediate reward reinforcement	Prosocial attitudes/behaviors; social decision making/pragmatic life knowledge

tivity.¹⁰⁹⁻¹¹³ Although not as often studied, regulation of positive emotions also seems to involve “top-down” prefrontal inhibition, although perhaps involving different subcortical regions, such as ventral striatum.¹¹³

Lieberman et al¹¹⁴ and others¹¹⁵ have also described a form of “unintentional self-regulation” or labeling negative emotions with words (“putting one’s feelings into words”). This action appears to increase ventrolateral PFC activity and decrease amygdala activity (similar to intentional cognitive reframing). A key overarching concept in emotional homeostasis is the ability of PFC to inhibit limbic reactivity.

Neurotransmitters and Genetics. As a personality trait, the heritability of impulsivity is approximately 45%.^{116,117} Dopamine, through its mesocortical pathway, modulates impulsivity, with many studies exploring this in the context of attention-deficit/hyperactivity disorder. The relationship between genetic variants of molecules involved in dopaminergic and serotonergic pathways and impulsivity is summarized in Table 1.

Monoamines have long been recognized as regulators of emotion, based largely on studies of psychiatric disorders. More recently, investigators have examined their roles in emotional regulation outside of the context of psychopathology per se, also summarized in Table 1.

Summary. Wisdom necessitates integration of cognitive and emotional functions. Emotional homeostasis has primarily been investigated in relation to downregulation of aversive emotions, often via PFC activation and associated dampening of amygdala activity. Controlling reactions to aversive stimuli is also related to optimal

monoaminergic functioning, especially variations related to dopamine and serotonin and genes associated with monoaminergic activity. The role of disinhibiting positive emotions in wisdom warrants further study.

Reflection/Self-understanding

Self-reflection is an essential prerequisite for insight, which is commonly included in many researchers’ concept of wisdom.

Brain Localization via Neuroimaging. Uddin and colleagues¹¹⁸ reviewed the concept of a “default mode” neural network, including dorsal and vmPFC, precuneus, and posterior-lateral cortices, that shows high metabolic activity at “baseline” or “rest.” This “rest” likely includes what has been termed *task-unrelated imagery and thought*, such as autobiographical reminiscence, self-referential thought, and inner speech. In neuroimaging studies, reflecting on one’s own current experience consistently activates MPFC. Tasks that involve self-judgment likewise activate MPFC.¹¹⁹ Autobiographical memories activate MPFC and vmPFC, compared with DLPFC activation in nonautobiographical episodic memory.¹²⁰ Although self-reflection in moderation likely fosters wisdom, there are other types of self-directed internal thought processes related to perseveration, obsessionality, or self-absorption that are antithetical to wisdom, and these may be moderated by lateral PFC.¹²¹

Summary. An interaction between medial and lateral PFC seems critical for appropriate self-reflection necessary for insight.

Value Relativism/Tolerance

Tolerance of other persons' or cultures' value systems is often considered an important subcomponent of wisdom.

Brain Localization via Neuroimaging. Neuroimaging studies of tolerance have frequently focused on prominent societal prejudices, especially those related to race/ethnicity. Some investigations have demonstrated that the regulation of "automatic" prejudicial responses follows a neurobiological pattern similar to that described for impulse control: dorsal ACC detects an undesirable attitude surfacing, prompting lateral PFC inhibition of undesirable attitudes, and leading to downstream amygdala deactivation.^{122,123} While sharing rudimentary neurobiology with impulse control, value relativism is conceptually more complex and its study would benefit from the development of novel measures/tasks. Notably, "theory of mind" studies suggest that lateral PFC lesions impair inhibition of focus on one's own experience, in turn impairing consideration of someone else's state of mind.^{121,124} Lieberman described how the ability to recognize others' views and values may be linked to lateral PFC inhibitory functions, stating

a failure of this process may play a role in 'naïve realism', when individuals assume that others see the world the same way as they do and have difficulty acknowledging alternative viewpoints.^{125(p263)}

Summary. Dorsal ACC and lateral PFC play important roles in tolerance of varied value systems by detecting and inhibiting, respectively, expressions of prejudicial responses.

Acknowledgment of and Dealing Effectively With Uncertainty and Ambiguity

Recognition and emotional tolerance of ambiguity, an important subcomponent of wisdom, have not received adequate attention in biological studies, although they may be partially related to factors described earlier for social decision making and emotional homeostasis.

Brain Localization via Neuroimaging. Krain and colleagues¹²⁶ reviewed neuroimaging studies of persons confronted with uncertain or ambiguous decisions and contrasted risk-based decision making (where outcomes have known probabilities and subjects choose between "safe" and "risky" decisions) vs decision making in the face of ambiguity (where the probability of specific outcomes is unknown or close to chance, and the choices do not differ in reward value). This meta-analysis concluded that decision making in the face of ambiguity most consistently activated DLPFC, dorsal ACC, insula, and parietal areas. In contrast, decisions involving risk activated OFC, MPFC, caudate, and rostral ACC. Subsequent investigations have supported this conclusion; persons who preferred ambiguous over risky decisions preferentially activated lateral PFC on fMRI.¹²⁷ Similarly, an fMRI study comparing ambiguous with unambiguous decisions found an association between ambiguity and dorsal ACC and DLPFC activity.¹²⁸ Overall, these results resonate with a concept proposed by Zelazo and Muller¹²⁹ that there is a

system for "hot" (ie, affectively charged) executive functions (consistent with regions activated in risk-based decision making) and "cold" (ie, analytical) executive functions (consistent with regions activated in decisions made amidst uncertainty).

Summary. Dorsal ACC and lateral PFC activity may be central to rational decision making in the face of ambiguity.

COMMENT

Wisdom is a long-recognized multidimensional and adaptive human attribute. By examining the more consistently identified subcomponents of wisdom, one can begin to hypothesize how such a complex human characteristic may be orchestrated within the human brain.

By using a definition of wisdom based on literature overview, as we have done, we risk relying on an averaged implicit theory of investigators rather than on a definitive model. However, a definitive model for a rather amorphous human trait may need empirical research demonstrating neurobiological basis for validated phenotypes. The ability to measure wisdom objectively is still quite limited, namely because the definition of wisdom is heterogeneous. To stimulate focused neurobiology research in wisdom, a provisional review-based definition serves a purpose, provided one recognizes this as only a first step in a long process.

This review also has other limitations. This was not a meta-analysis and may have overlooked some relevant articles. Furthermore, there may be disagreement regarding the definition and measurement of some of the proposed subcomponents of wisdom. The biological investigations reviewed did not explicitly propose to study wisdom. Many studies included performance-based laboratory tasks, whose validity for assessing specific domains of wisdom may be open to question (eg, how well an in vitro game assesses altruism in real life). A number of studies used fMRI; there are several common limitations to this research, including small sample sizes, difficulty interpreting connectivity or circuitry from isolated regional changes, variations in anatomical definitions of PFC subdivisions, and direct measurement of blood flow rather than neuronal function. Finally, published investigations on neurotransmitters and genetics in relationship to certain subcomponents of wisdom were scarce.

Nonetheless, several common themes from the reviewed biological studies can be summarized (Table 2). Although data on connectivity in the neuroimaging studies are limited, using the available evidence, we propose a working model, admittedly speculative, of how specific brain regions may interact to contribute to subcomponents of wisdom (**Figure 3**). The lateral PFC (especially DLPFC), often working in concert with dorsal ACC and at times with OFC and MPFC, appears to have an important inhibitory effect on several brain areas associated with emotionality and immediate reward dependence (eg, amygdala, ventral striatum), thereby facilitating the subcomponents described as pragmatic life knowledge and decision making, emotional homeostasis, value relativism, and processing ambiguity. This ra-

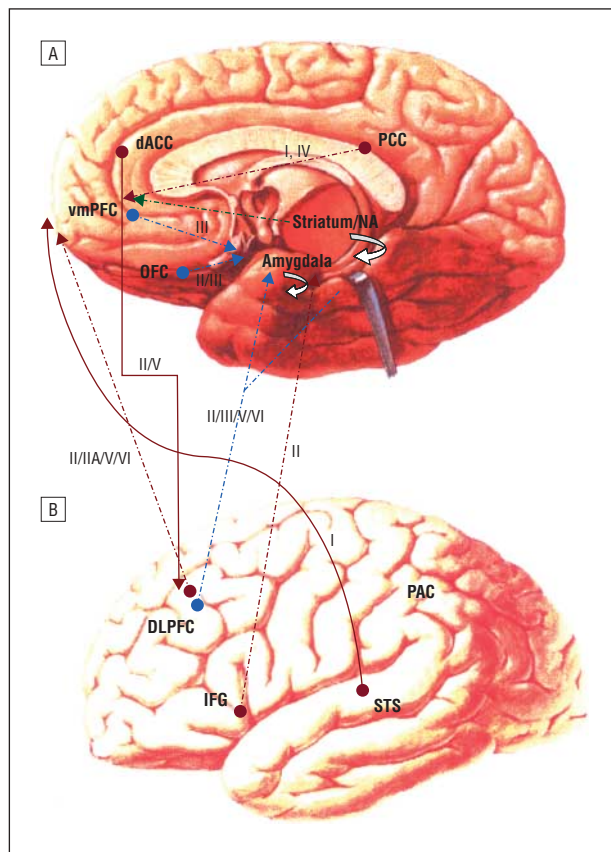


Figure 3. The medial (A) and lateral (B) surfaces of the human cerebral hemispheres. Curved arrows indicate structures not externally visible on this cross-section. The following Roman numerals indicate wisdom components and putative pathways that may be involved in their regulation: I, prosocial attitudes/behaviors; II, pragmatic decision making based on delayed over immediate gratification; III, promotes utilitarian moral decisions; IV, self-reflection in moderation that contributes to wisdom; V, value relativism/consideration of others' point of view; and VI, tolerance of ambiguity. Monoaminergic/neuropeptide regulation: dorsal anterior cingulate cortex (dACC); dopaminergic regulation: dorsolateral prefrontal cortex (DLPFC); excitatory: inferior frontal gyrus (IFG); and inhibitory: nucleus accumbens (NA), orbitofrontal cortex (OFC), parietal association cortices (PAC), posterior cingulate cortex (PCC), and superior temporal sulcus (STS). vmPFC indicates ventromedial prefrontal cortex.

tional/analytical aspect of wisdom appears to be complemented by a more emotion-based subcomponent, including prosocial attitudes and behaviors that involve MPFC, PCC, OFC, superior temporal sulcus, and reward neurocircuitry. Likewise, MPFC seems to mediate self-reflection and self-awareness; a certain amount of lateral PFC inhibition of this process may, however, be required to stop this function short of maladaptive self-absorption. It is interesting to note the interplay and balance between phylogenetically older brain regions (eg, limbic cortex) and the more recently evolved PFC in the putative neurobiology of wisdom.

Our suggested model of the neurobiology of wisdom raises a conceptual issue. How can our holistic concept of wisdom as a distinct trait, which is consistent with the unified theory of mind,¹³⁰ be compatible with the reductionism implicit in the relationship between individual brain regions and specific mental functions hypothesized in the neuroimaging research reviewed earlier? We believe that these 2 perspectives can coexist, just as

Takahashi and Overton⁵ have sought to integrate the analytic and synthetic models of wisdom. Examining functional divisions in the brain via fMRI and similar methods is potentially valuable. For example, Jung and Haier¹³¹ recently reviewed neuroimaging studies relevant to human intelligence and reasoning. They concluded that there are several distinct brain regions that contribute to intelligence and reasoning and that the coordination among these regions appears to follow a pattern they termed *parieto-frontal integration*. As expected, there is partial overlap in the brain regions (eg, ACC, DLPFC) implicated in their review and ours. Nonetheless, there are several important characteristics in which wisdom differs from intelligence and reasoning in that it also includes domains such as practical application of knowledge, use of knowledge for the common social good, and integration of affect and knowledge.^{12,132} Brain regions putatively involved in wisdom that were not prominent in the review of intelligence and reasoning¹³¹ include limbic cortex, MPFC, and striatum. Although there is general agreement regarding important functional divisions within the brain, the nature of these divisions is almost assuredly oversimplified and will undergo continual revisions.⁵ The same would apply to specific subcomponents of wisdom.

The possible neurochemical and genetic contributions to wisdom (Table 1) are related to many of those identified in psychopathology. The fact that monoaminergic functioning is related to stress reactivity and emotional homeostasis is not surprising. The possible roles of oxytocin and vasopressin in prosocial behaviors demonstrate the importance of examining nontraditional neurotransmitters.

Empirical research on wisdom is in its infancy. There are several potentially valuable lines of research that may be suggested.

1. *Defining a valid phenotype:* Reliability and validity of theory-based definitions of wisdom should be demonstrated across different populations.

2. *Objectively measuring wisdom:* Relatively objective, reliable measures of real-world behaviors should be developed.

3. *Investigating developmental course of wisdom:* Wisdom may be studied from a developmental perspective to identify possible critical periods for wisdom development. Advances in genetics/genomics and connectivity analyses in functional neuroimaging as well as electrophysiology may help clarify the interplay between biological and environmental factors in the lifetime course of wisdom.

4. *Examining relationship of wisdom to sociodemographic variables:* Older age has been traditionally associated with wisdom but the limited available empirical research does not consistently support this notion.¹³³⁻¹³⁵ The neurobiological literature is sparse regarding age-related differences in most of the subcomponents of wisdom discussed. One notable exception is that aging has been associated with better emotional regulation.¹³⁶ The possible enhancement of wisdom and its specific subcomponents with aging-related cumulative life experience warrants investigation. Cross-cultural compari-

sons of wisdom and sex differences also deserve research.

5. *Studying neuropsychiatric disorders affecting wisdom*: Research in naturally occurring disorders (eg, frontotemporal dementia¹³⁷ or traumatic injuries [eg, case of Phineas Gage])¹³⁸ that affect the implicated neurobiological substrates of wisdom would help inform the neurobiology of wisdom as well as clinical applications of the concept.

6. *Using animal models*: While wisdom may be uniquely human, certain intermediate phenotypes could be studied in appropriate animal models.

7. *Assessing health care implications of wisdom*: Research on possible impact of wisdom on longevity, quality of life, and receipt of improved health care would have major public health significance.

8. *Developing interventions to enhance wisdom*: Development and testing of interventions (psychosocial or biological) to enhance wisdom could be valuable for people with and without serious psychopathology. Similarly, whether wisdom moderates the outcomes of other interventions (eg, psychotherapy) would be useful to evaluate.

Wisdom warrants scientific study with the same rigorous methods that we demand in investigations on various forms of psychopathology. At the same time, progress in such research will require maintaining the wisdom to recognize the limits of available scientific methods.

Submitted for Publication: June 17, 2008; final revision received October 2, 2008; accepted October 6, 2008.

Correspondence: Dilip V. Jeste, MD, Division of Geriatric Psychiatry, University of California, San Diego, 116A-1, VA San Diego Healthcare System, 3350 La Jolla Village Dr, San Diego, CA 92161 (djeste@ucsd.edu).

Financial Disclosure: None reported.

Funding/Support: This work was supported, in part, by grant MH080002 from the National Institute of Mental Health, grant AG26757 from the National Institute on Aging, the US Health Resources and Services Administration (Geriatric Academic Career Award), and by the University of California, San Diego, Sam and Rose Stein Institute for Research on Aging and the Department of Veterans Affairs.

REFERENCES

1. Aquinas T. *Summa contra Gentiles*. Notre Dame, IN: University of Notre Dame Press; 1991.
2. Takahashi M. Toward a culturally inclusive understanding of wisdom: historical roots in the East and West. *Int J Aging Hum Dev*. 2000;51(3):217-230.
3. *Webster's Encyclopedic Dictionary of the English Language*. New York, NY: Lexicon Publications; 1990.
4. Jeste DV, Vahia I. Comparison of the conceptualization of wisdom in ancient Indian literature with modern views: focus on the Bhagavad Gita. *Psychiatry*. 2008;71(3):197-209.
5. Takahashi M, Overton WF. Cultural foundations of wisdom: an integrated developmental approach. In: Sternberg RJ, Jordan J, eds. *A Handbook of Wisdom: Psychological Perspectives*. New York, NY: Cambridge University Press; 2005:32-60.
6. Birren JE, Svensson CM. Wisdom in history. In: Sternberg RJ, Jordan J, eds. *A Handbook of Wisdom: Psychological Perspectives*. New York, NY: Cambridge University Press; 2005:3-31.
7. Brugman GM. *Wisdom and Aging*. Amsterdam, Netherlands: Elsevier; 2006.
8. Ardel M. Wisdom as expert knowledge system: a critical review of a contemporary operationalization of an ancient concept. *Hum Dev*. 2004;47(5):257-285.
9. Zola-Morgan S. Localization of brain function: the legacy of Franz Joseph Gall (1758-1828). *Annu Rev Neurosci*. 1995;18:359-383.
10. Rosel N. Clarification and application of Erik Erikson's eighth stage of man. *Int J Aging Hum Dev*. 1988;27(1):11-23.
11. Baltes PB, Smith J, Staudinger UM. Wisdom and successful aging. *Nebr Symp Motiv*. 1991;39:123-167.
12. Clayton V. Wisdom and intelligence: the nature and function of knowledge in the later years. *Int J Aging Hum Dev*. 1982;15(4):315-321.
13. Sternberg RJ. *Wisdom: Its Nature, Origins, and Development*. New York, NY: Cambridge University Press; 1990.
14. Ardel M. Empirical assessment of a three-dimensional wisdom scale. *Res Aging*. 2003;25(3):275-324.
15. Vaillant GE. Mental health. *Am J Psychiatry*. 2003;160(8):1373-1384.
16. Tucker PM, Pfefferbaum B, North CS, Kent A, Burgin CE, Parker DE, Hossain A, Jeon-Slaughter H, Trautman RP. Physiologic reactivity despite emotional resilience several years after direct exposure to terrorism. *Am J Psychiatry*. 2007;164(2):230-235.
17. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82.
18. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry*. 2004;161(2):195-216.
19. Blazer DG. Successful aging. *Am J Geriatr Psychiatry*. 2006;14(1):2-5.
20. Vaillant GE. *Does Wisdom Increase With Age? Aging Well: Surprising Guideposts to a Happier Life From the Landmark Harvard Study of Adult Development*. Boston, MA: Little, Brown and Co; 2002:249-257.
21. Brugman GM. Wisdom and aging. In: Birren JE, Schaie KW, eds. *Handbook of the Psychology of Aging*. 6th ed. Burlington, MA: Elsevier Academic Press; 2005:445-469.
22. Jason LA, Reichler A, King C, Madsen D, Camacho J, Marchese W. The measurement of wisdom: a preliminary report. *J Community Psychol*. 2001;29(5):585-598.
23. Hall SS. The older-and-wiser hypothesis. *New York Times*. May 6, 2007. <http://www.nytimes.com/2007/05/06/magazine/06Wisdom-t.html>. Accessed January 6, 2009.
24. Hergott LJ. A piece of my mind. Playing the Moonlight Sonata from memory: celebrating the wonders of our difficult life. *JAMA*. 2002;288(20):2516-2517.
25. Keeley D. Rigorous assessment of palliative care revisited: wisdom and compassion are needed when evidence is lacking. *BMJ*. 1999;319(7223):1447-1448.
26. Daniele F. First International Conference between West and East—Leonardo and Lao-Tze: Western science meets Eastern wisdom. Experiences of scientists and intellectuals for the creation of a new paradigm of modern science. *Evid Based Complement Alternat Med*. 2008;5(1):51-54.
27. Nemiroff GH. *Reconstructing Education: Toward a Pedagogy of Critical Humanism*. New York, NY: Bergin and Garvey; 1992.
28. Glover RJ. Perspectives on aging: issues affecting the latter part of the life cycle. *Educ Gerontol*. 1998;24(4):325-331.
29. Brown SC, Greene JA. The Wisdom Development Scale: translating the conceptual to the concrete. *J Coll Student Dev*. 2008;47(1):1-19.
30. Baltes PB, Staudinger UM. Wisdom: a metaheuristic (pragmatic) to orchestrate mind and virtue toward excellence. *Am Psychol*. 2000;55(1):122-136.
31. Vaillant GE, Mukamal K. Successful aging. *Am J Psychiatry*. 2001;158(6):839-847.
32. Eisenberg N. Empathy-related responding and prosocial behaviour. *Novartis Found Symp*. 2007;278:71-80.
33. de Waal FB. Putting the altruism back into altruism: the evolution of empathy. *Annu Rev Psychol*. 2008;59:279-300.
34. di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: a neurophysiological study. *Exp Brain Res*. 1992;91(1):176-180.
35. Craighero L, Metta G, Sandini G, Fadiga L. The mirror-neurons system: data and models. *Prog Brain Res*. 2007;164:39-59.
36. Decety J, Jackson PL. The functional architecture of human empathy. *Behav Cogn Neurosci Rev*. 2004;3(2):71-100.
37. Pfeifer JH, Iacoboni M, Mazziotta JC, Dapretto M. Mirroring others' emotions relates to empathy and interpersonal competence in children. *Neuroimage*. 2008;39(4):2076-2085.
38. Perner J, Lang B. Development of theory of mind and executive control. *Trends Cogn Sci*. 1999;3(9):337-344.
39. Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RS, Frith CD. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. *Cognition*. 1995;57(2):109-128.

40. Gallagher HL, Happé F, Brunswick N, Fletcher PC, Frith CD, Frith CD. Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. *Neuropsychologia*. 2000;38(1):11-21.
41. Goel V, Grafman J, Sadato N, Hallett M. Modeling other minds. *Neuroreport*. 1995;6(13):1741-1746.
42. Brunet E, Sarfati Y, Hardy-Bayle MC, Decety JA. PET investigation of the attribution of intentions with a nonverbal task. *Neuroimage*. 2000;11(2):157-166.
43. Seitz RJ, Schäfer R, Scherfeld D, Friederichs S, Popp K, Wittsack HJ, Azari NP, Franz M. Valuating other people's emotional face expression: a combined functional magnetic resonance imaging and electroencephalography study. *Neuroscience*. 2008;152(3):713-722.
44. Seitz RJ, Nickel J, Azari NP. Functional modularity of the medial prefrontal cortex: involvement in human empathy. *Neuropsychology*. 2006;20(6):743-751.
45. Farrow TF, Zheng Y, Wilkinson ID, Spence SA, Deakin JF, Tarriner N, Griffiths PD, Woodruff PW. Investigating the functional anatomy of empathy and forgiveness. *Neuroreport*. 2001;12(11):2433-2438.
46. Shamay-Tsoory SG, Tomer R, Berger BD, Aharon-Peretz J. Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *J Cogn Neurosci*. 2003;15(3):324-337.
47. Lawrence EJ, Shaw P, Giampietro VP, Surguladze S, Brammer MJ, David AS. The role of 'shared representations' in social perception and empathy: an fMRI study. *Neuroimage*. 2006;29(4):1173-1184.
48. De Dreu CK, Weingart LR, Kwon S. Influence of social motives on integrative negotiation: a meta-analytic review and test of two theories. *J Pers Soc Psychol*. 2000;78(5):889-905.
49. Rilling J, Gutman D, Zeh T, Pagnoni G, Berns G, Kilts C. A neural basis for social cooperation. *Neuron*. 2002;35(2):395-405.
50. Decety J, Jackson PL, Sommerville JA, Chaminade T, Meltzoff AN. The neural bases of cooperation and competition: an fMRI investigation. *Neuroimage*. 2004;23(2):744-751.
51. Singer T, Kiebel SJ, Winston JS, Dolan RJ, Frith CD. Brain responses to the acquired moral status of faces. *Neuron*. 2004;41(4):653-662.
52. de Quervain DJ, Fischbacher U, Treyer V, Schellhammer M, Schnyder U, Buck A, Fehr E. The neural basis of altruistic punishment. *Science*. 2004;305(5688):1254-1258.
53. Rilling JK, Sanfey AG, Aronson JA, Nystrom LE, Cohen JD. Opposing BOLD responses to reciprocated and unreciprocated altruism in putative reward pathways. *Neuroreport*. 2004;15(16):2539-2543.
54. Rilling JK, Glenn AL, Jairam MR, Pagnoni G, Goldsmith DR, Effenbein HA, Liliensfeldt SO. Neural correlates of social cooperation and non-cooperation as a function of psychopathy. *Biol Psychiatry*. 2007;61(11):1260-1271.
55. Lehmann L, Keller L. The evolution of cooperation and altruism—a general framework and a classification of models. *J Eval Biol*. 2006;19(5):1365-1376.
56. Harbaugh WT, Mayr U, Burghart DR. Neural responses to taxation and voluntary giving reveal motives for charitable donations. *Science*. 2007;316(5831):1622-1625.
57. Moll J, Krueger F, Zahn R, Pardini M, Oliveira-Souza R, Grafman J. Human fronto-mesolimbic networks guide decisions about charitable donation. *Proc Natl Acad Sci U S A*. 2006;103(42):15623-15628.
58. Hur YM, Rushton JP. Genetic and environmental contributions to prosocial behaviour in 2- to 9-year-old South Korean twins. *Biol Lett*. 2007;3(6):664-666.
59. Rushton JP. Genetic and environmental contributions to pro-social attitudes: a twin study of social responsibility. *Proc Biol Sci*. 2004;271(1557):2583-2585.
60. Rushton JP, Fulker DW, Neale MC, Nias DK, Eysenck HJ. Altruism and aggression: the heritability of individual differences. *J Pers Soc Psychol*. 1986;50(6):1192-1198.
61. Bachner-Melman R, Gritsenko I, Nemanov L, Zohar AH, Dina C, Ebstein RP. Dopaminergic polymorphisms associated with self-report measures of human altruism: a fresh phenotype for the dopamine D4 receptor. *Mol Psychiatry*. 2005;10(4):333-335.
62. Reeves SJ, Mehta MA, Montgomery AJ, Amiras D, Egerton A, Howard RJ, Grasby PM. Striatal dopamine (D2) receptor availability predicts socially desirable responding. *Neuroimage*. 2007;34(4):1782-1789.
63. Young SE, Smolen A, Hewitt JK, Haberstick BC, Stallings MC, Corley RP, Crowley TJ. Interaction between MAO-A genotype and maltreatment in the risk for conduct disorder: failure to confirm in adolescent patients. *Am J Psychiatry*. 2006;163(6):1019-1025.
64. Wood RM, Rilling JK, Sanfey AG, Bhagwager Z, Rogers RD. Effects of tryptophan depletion on the performance of an iterated Prisoner's Dilemma game in healthy adults. *Neuropsychopharmacology*. 2006;31(5):1075-1084.
65. Knafo A, Israel S, Darvasi A, Bachner-Melman R, Uzevovskiy F, Cohen L, Feldman E, Lerer E, Laiba E, Raz Y, Nemanov L, Gritsenko I, Dina C, Agam G, Dean B, Bornstein G, Ebstein RP. Individual differences in allocation of funds in the dictator game associated with length of the arginine vasopressin 1a receptor RS3 promoter region and correlation between RS3 length and hippocampal mRNA. *Genes Brain Behav*. 2008;7(3):266-275.
66. Jacob S, Brune CW, Carter CS, Leventhal BL, Lord C, Cook EH Jr. Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neurosci Lett*. 2007;417(1):6-9.
67. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001;158(7):1052-1057.
68. Cornish KM, Manly T, Savage R, Swanson J, Morisano D, Butler N, Grant C, Cross G, Bentley L, Hollis CP. Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. *Mol Psychiatry*. 2005;10(7):686-698.
69. Eisenberg J, Mei-Tal G, Steinberg A, Tartakovsky E, Zohar A, Gritsenko I, Nemanov L, Ebstein RP. Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. *Am J Med Genet*. 1999;88(5):497-502.
70. Drabant EM, Hariri AR, Meyer-Lindenberg A, Munoz KE, Mattay VS, Kolachana BS, Egan MF, Weinberger DR. Catechol O-methyltransferase val158met genotype and neural mechanisms related to affective arousal and regulation. *Arch Gen Psychiatry*. 2006;63(12):1396-1406.
71. Nomura M, Nomura Y. Psychological, neuroimaging, and biochemical studies on functional association between impulsive behavior and the 5-HT2A receptor gene polymorphism in humans. *Ann N Y Acad Sci*. 2006;1086:134-143.
72. Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang Y, Hwang DR, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever LJ. Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [¹¹C]McN 5652. *Am J Psychiatry*. 2005;162(5):915-923.
73. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri A, Pezawas L, Blasi G, Wabnitz A, Honea R, Verchinski B, Callicott JH, Egan M, Mattay V, Weinberger DR. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci U S A*. 2006;103(16):6269-6274.
74. Passamonti L, Fera F, Magariello A, Cerasa A, Gioia MC, Muglia M, Nicoletti G, Gallo O, Provinciali L, Quattrone A. Monoamine oxidase-a genetic variations influence brain activity associated with inhibitory control: new insight into the neural correlates of impulsivity. *Biol Psychiatry*. 2006;59(4):334-340.
75. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297(5580):400-403.
76. Heinz A, Braus DF, Smolka MN, Wrase J, Puls I, Hermann D, Klein S, Grüsser SM, Flor H, Schumann G, Mann K, Büchel C. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci*. 2005;8(1):20-21.
77. Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR. A susceptibility gene for affective disorders and the response of the human amygdala. *Arch Gen Psychiatry*. 2005;62(2):146-152.
78. Canli T, Omura K, Haas BW, Fallgatter A, Constable RT, Lesch KP. Beyond affect: a role for genetic variation of the serotonin transporter in neural activation during a cognitive attention task. *Proc Natl Acad Sci U S A*. 2005;102(34):12224-12229.
79. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005;8(6):828-834.
80. David SP, Murthy NV, Rabiner EA, Munafó MR, Johnstone EC, Jacob R, Walton RT, Grasby PM. A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans. *J Neurosci*. 2005;25(10):2586-2590.
81. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5HTT gene. *Science*. 2003;301(5631):386-389.
82. Canli T, Qiu M, Omura K, Congdon E, Haas BW, Amin Z, Herrmann MJ, Constable RT, Lesch KP. Neural correlates of epigenesis. *Proc Natl Acad Sci U S A*. 2006;103(43):16033-16038.
83. Gutknecht L, Jacob C, Strobel A, Kriegebaum C, Müller J, Zeng Y, Markert C, Escher A, Wendland J, Reif A, Mossner R, Gross C, Brocke B, Lesch KP. Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation. *Int J Neuropsychopharmacol*. 2007;10(3):309-320.
84. Canli T, Congdon E, Gutknecht L, Constable RT, Lesch KP. Amygdala responsiveness is modulated by tryptophan hydroxylase-2 gene variation. *J Neural Transm*. 2005;112(11):1479-1485.
85. Herrmann MJ, Huter T, Müller F, Muhlberger A, Pauli P, Reif A, Renner T, Canli T, Fallgatter AJ, Lesch KP. Additive effects of serotonin transporter and trypt-

- tophan hydroxylase-2 gene variation on emotional processing. *Cereb Cortex*. 2007;17(5):1160-1163.
86. Neumeister A, Charney DS, Belfer I, Geraci M, Holmes C, Sharabi Y, Alim T, Bonne O, Luckenbaugh DA, Manji H, Goldman D, Goldstein DS. Sympathoneural and adrenergic functional effects of alpha2C-adrenoreceptor gene polymorphism in healthy humans. *Pharmacogenet Genomics*. 2005;15(3):143-149.
 87. Morgan CA III, Wang S, Rasmusson A, Hazlett G, Anderson G, Charney DS. Relationship among plasma cortisol, catecholamines, neuropeptide Y, and human performance during exposure to uncontrollable stress. *Psychosom Med*. 2001;63(3):412-422.
 88. Baltes PB, Smith J, Staudinger UM. Wisdom and successful aging. In: Son-deregger T, ed. *Nebraska Symposium on Motivation*. Lincoln: University of Nebraska Press; 1992:123-167.
 89. Ernst M, Paulus MP. Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. *Biol Psychiatry*. 2005;58(8):597-604.
 90. Montague PR, Berns GS. Neural economics and the biological substrates of valuation. *Neuron*. 2002;36(2):265-284.
 91. Osbeck LM, Robinson DN. Philosophical theories of wisdom. In: Sternberg RJ, Jordan J, eds. *A Handbook of Wisdom: Psychological Perspectives*. New York, NY: Cambridge University Press; 2005:3-31.
 92. McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. *Science*. 2004;306(5695):503-507.
 93. Boettiger CA, Mitchell JM, Tavares VC, Robertson M, Joslyn G, D'Esposito M, Fields HL. Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-O-methyltransferase 158(Val/Val) genotype. *J Neurosci*. 2007;27(52):14383-14391.
 94. Berlin HA, Rolls ET, Kischka U. Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*. 2004;127(pt 5):1108-1126.
 95. Eshel N, Nelson EE, Blair RJ, Pine DS, Ernst M. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. *Neuropsychologia*. 2007;45(6):1270-1279.
 96. Robertson D, Snarey J, Ousley O, Harenski K, DuBois BF, Gilkey R, Kilts C. The neural processing of moral sensitivity to issues of justice and care. *Neuropsychologia*. 2007;45(4):755-766.
 97. Luo Q, Nakic M, Wheatley T, Richell R, Marton A, Blair RJ. The neural basis of implicit moral attitude—an IAT study using event-related fMRI. *Neuroimage*. 2006;30(4):1449-1457.
 98. Greene JD, Sommerville RB, Nystrom LE, Darley JM, Cohen JD. An fMRI investigation of emotional engagement in moral judgment. *Science*. 2001;293(5537):2105-2108.
 99. Heekeren HR, Wartenburger I, Schmidt H, Schwintowski HP, Villringer A. An fMRI study of simple ethical decision-making. *Neuroreport*. 2003;14(9):1215-1219.
 100. Pujol J, Reixach J, Harrison BJ, Timoneda-Gallart C, Vilanova JC, Perez-Alvarez F. Posterior cingulate activation during moral dilemma in adolescents. *Hum Brain Mapp*. 2008;29(8):910-921.
 101. Greene JD, Nystrom LE, Engell AD, Darley JM, Cohen JD. The neural bases of cognitive conflict and control in moral judgment. *Neuron*. 2004;44(2):389-400.
 102. Koenigs M, Young L, Adolphs R, Tranel D, Cushman F, Hauser M, Damasio A. Damage to the prefrontal cortex increases utilitarian moral judgements. *Nature*. 2007;446(7138):908-911.
 103. Green MF, Penn DL, Bentall R, Carpenter WT, Gaebel W, Gur RC, Kring AM, Park S, Silverstein SM, Heinssen R. Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. *Schizophr Bull*. 2008;34(6):1211-1220.
 104. Abu-Akel A. The neurochemical hypothesis of 'theory of mind'. *Med Hypotheses*. 2003;60(3):382-386.
 105. Vaillant G. *Spiritual Evolution: A Scientific Defense of Faith*. New York, NY: Broadway; 2008.
 106. Congdon E, Canli T. The endophenotype of impulsivity: reaching concisience through behavioral, genetic, and neuroimaging approaches. *Behav Cogn Neurosci Rev*. 2005;4(4):262-281.
 107. Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci*. 2003;6(2):115-116.
 108. Horn NR, Dolan M, Elliott R, Deakin JF, Woodruff PW. Response inhibition and impulsivity: an fMRI study. *Neuropsychologia*. 2003;41(14):1959-1966.
 109. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhdé TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2005;57(3):210-219.
 110. Goldin PR, McRae K, Ramel W, Gross JJ. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biol Psychiatry*. 2008;63(6):577-586.
 111. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci*. 2002;14(8):1215-1229.
 112. Cooney RE, Joormann J, Atlas LY, Eugène F, Gotlib IH. Remembering the good times: neural correlates of affect regulation. *Neuroreport*. 2007;18(17):1771-1774.
 113. Kim SH, Hamann S. Neural correlates of positive and negative emotion regulation. *J Cogn Neurosci*. 2007;19(5):776-798.
 114. Lieberman MD, Eisenberger NI, Crockett MJ, Tom SM, Pfeifer JH, Way BM. Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol Sci*. 2007;18(5):421-428.
 115. Hariiri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport*. 2000;11(1):43-48.
 116. Pedersen NL, Plomin R, McClearn GE, Friberg L. Neuroticism, extraversion, and related traits in adult twins reared apart and reared together. *J Pers Soc Psychol*. 1988;55(6):950-957.
 117. Seroczynski AD, Bergeman CS, Coccaro EF. Etiology of the impulsivity/aggression relationship: genes or environment? *Psychiatry Res*. 1999;86(1):41-57.
 118. Uddin LQ, Iacoboni M, Lange C, Keenan JP. The self and social cognition: the role of cortical midline structures and mirror neurons. *Trends Cogn Sci*. 2007;11(4):153-157.
 119. Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, Mayberg H. In search of the emotional self: an fMRI study using positive and negative emotional words. *Am J Psychiatry*. 2003;160(11):1938-1945.
 120. Gilboa A. Autobiographical and episodic memory—one and the same? Evidence from prefrontal activation in neuroimaging studies. *Neuropsychologia*. 2004;42(10):1336-1349.
 121. Samson D, Apperly IA, Kathirgamanathan U, Humphreys GW. Seeing it my way: a case of a selective deficit in inhibiting self-perspective. *Brain*. 2005;128(pt 5):1102-1111.
 122. Amodio DM, Harmon-Jones E, Devine PG, Curtin JJ, Hartley SL, Covert AE. Neural signals for the detection of unintentional race bias. *Psychol Sci*. 2004;15(2):88-93.
 123. Cunningham WA, Johnson MK, Raye CL, Chris GJ, Gore JC, Banaji MR. Separable neural components in the processing of black and white faces. *Psychol Sci*. 2004;15(12):806-813.
 124. Samson D, Apperly IA, Humphreys GW. Error analyses reveal contrasting deficits in "theory of mind": neuropsychological evidence from a 3-option false belief task. *Neuropsychologia*. 2007;45(11):2561-2569.
 125. Lieberman MD. Social cognitive neuroscience: a review of core processes. *Annu Rev Psychol*. 2007;58:259-289.
 126. Krain AL, Wilson AM, Ar buckle R, Castellanos FX, Milham MP. Distinct neural mechanisms of risk and ambiguity: a meta-analysis of decision-making. *Neuroimage*. 2006;32(1):477-484.
 127. Huettel SA, Stowe CJ, Gordon EM, Warner BT, Platt ML. Neural signatures of economic preferences for risk and ambiguity. *Neuron*. 2006;49(5):765-775.
 128. Simmons A, Stein MB, Matthews SC, Feinstein JS, Paulus MP. Affective ambiguity for a group recruits ventromedial prefrontal cortex. *Neuroimage*. 2006;29(2):655-661.
 129. Zelazo PD, Muller U. Executive function in typical and atypical development. In: Goswami U, ed. *Handbook of Childhood Cognitive Development*. Oxford, England: Blackwell; 2002:445-489.
 130. Uttal WR. A credo for a revitalized behaviorism: characteristics and emerging principles. *Behav Processes*. 2001;54(1-3):5-10.
 131. Jung RE, Haier RJ. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *Behav Brain Sci*. 2007;30(2):135-154.
 132. Sternberg RJ. A systems model of leadership: WICS. *Am Psychol*. 2007;62(1):34-42.
 133. Baltes PB, Staudinger U, Maercker A, Smith J. People nominated as wise: a comparative study of wisdom related knowledge. *Psychol Aging*. 1995;10(2):155-166.
 134. Staudinger UM, Baltes PB. Interactive minds: a facilitative setting for wisdom-related performance. *J Pers Soc Psychol*. 1996;71(4):746-762.
 135. Smith J, Baltes PB. Profiles of psychological functioning in the old and oldest old. *Psychol Aging*. 1997;12(3):458-472.
 136. Mather M, Cartensen LL. Aging and motivated cognition: the positivity effect in attention and memory. *Trends Cogn Sci*. 2005;9(10):496-502.
 137. Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry*. 2008;69(1):60-73.
 138. Haas LF. Phineas Gage and the science of brain localisation. *J Neurol Neurosurg Psychiatry*. 2001;71(6):761.