Neurobiology of Wisdom

A Literature Overview

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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

Wisdom, 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. A standard philosophical (in Greek, philosophy = lover of wisdom) definition of wisdom pertains to judicious application of knowledge, 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. 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.

In the 19th century, Gall, who popularized the pseudoscience of phrenology,
included among its 27 mental functions “comparative sagacity,” at times called wisdom, and assigned it to prefrontal regions. 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. Erikson 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., Clayton, and others initiated empirical research in this area. Although the initial western theories of wisdom focused on cognitive abilities, Ardel suggested other domains of wisdom, such as religiosity, intuition, or epistemology, should be considered as well.

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

Although there is no consensus 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. Although 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 and 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 1. The numbers of publications from a PubMed search from January 1970 through April 2008 that addressed wisdom as a psychological or cognitive construct.

Figure 2. Commonly proposed subcomponents of wisdom.
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 attribute\textsuperscript{30} restricted to iconic individuals like Mother Teresa, Mahatma Gandhi, and Nelson Mandela.\textsuperscript{3} 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.\textsuperscript{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.\textsuperscript{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 facilitates other prosocial behaviors, including altruism.\textsuperscript{32,33} Mirror neurons, originally discovered in primates\textsuperscript{34} 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.\textsuperscript{35} Persons with greater unconscious somatic mimicry have higher ratings of self-reported altruism.\textsuperscript{36} When children observe and imitate facial expressions, mirror neurons are activated, and this activity correlates with empathy scores.\textsuperscript{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 Lang\textsuperscript{38} 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.\textsuperscript{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.\textsuperscript{43} A meta-analysis of 80 studies concluded that MPFC had a prominent role in empathy.\textsuperscript{44} Individuals activate MPFC while making empathic social judgments,\textsuperscript{45} and ventromedial PFC (vmPFC) lesions predict empathic deficits.\textsuperscript{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.\textsuperscript{47}

**Social Cooperation.** Social cooperation (vs competition) likewise appears related to prosocial motives\textsuperscript{48} 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.\textsuperscript{49-51} Likewise, “altruistic punishment” (punishment of violators of social norms at cost to oneself) activates reward neurocircuitry.\textsuperscript{52} In contrast, social competition either decreases activity in areas activated by cooperation\textsuperscript{53} or activates other regions such as DLPFC.\textsuperscript{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...
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.

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 al98 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.90 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(98) 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 MRI. 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.97 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

Neurotransmitters and Genetics. Several genetic studies have reported that the heritability of prosocial behaviors, including altruism, is 50% to 60%.97,103,104 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.
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 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 1. Neurotransmitter Variants Associated With 2 Proposed Subcomponents of Wisdom: Prosocial Attitudes/Behaviors and Emotional Homeostasis

<table>
<thead>
<tr>
<th>Wisdom Subcomponent</th>
<th>Neurotransmitter</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Prosocial attitudes/behaviors</td>
<td>Dopamine</td>
<td>DRD1 and DRD2 polymorphisms associated with self-reported selflessness61; striatal DRD1 receptor binding potential correlated with increased socially desirable responses62</td>
</tr>
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<td></td>
<td>Serotonin</td>
<td>MAO-A polymorphisms associated with antisocial personality features63; decreased social cooperation in the Prisoner’s Dilemma game (testing social cooperation) following dietary tryptophan depletion64</td>
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<td>Vasopressin</td>
<td>Strongly related to affiliative behavior in small mammals called voles; longer repeats in the RS3 promoter region of the AVPR1a gene in humans were associated with more altruistic actions in an in vivo game, higher self-reported altruism, and higher levels of postmortem AVPR1a messenger RNA65</td>
</tr>
<tr>
<td>Emotional homeostasis (including low impulsivity)</td>
<td>Oxytocin</td>
<td>DRD4, DAT, and COMT polymorphisms linked to risk for ADHD and/or measures of impulsivity66-69; 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/OF and amygdala/hippocampus70</td>
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<td>Polymorphism in the 5HT1A receptor gene associated with variations in impulsivity scores as measured by go/no-go tasks71; decreased availability of the serotonin transporter in anterior cingulate in persons with impulsive aggression vs comparison subjects72; 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 impulsivity73,74; the (s) allele of 5HTT promoter region associated with decreased production of 5HTT and increased amygdala activity in response to emotional (vs neutral) stimuli75-78; 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 5HT1A 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 stressors80-82; (7) allele of TH2-2, 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 (7) allele and 5HTT (s) allele83-85</td>
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<td></td>
<td>Norepinephrine</td>
<td>Polymorphism in α2-adrenergic receptor gene associated with elevated sympathetic and adrenomedullary responses to induced stress86; 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 performance87</td>
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</table>

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.
The heritability of impulsivity is approximately 45%.

Limbic reactivity. In emotional homeostasis is the ability of PFC to inhibit reactive 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 of "unintentional self-regulation" or labeling negative emotions also seems critical for appropriate self-reflection necessary for insight.

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.

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

<table>
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<th>Associated Cognitive/Emotional Tasks</th>
<th>Putative Subcomponents of Wisdom Served</th>
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<td>Anterior cingulate cortex</td>
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Neurotransmitters and Genetics. As a personality trait, the heritability of impulsivity is approximately 45%. 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.

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

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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.

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%. 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.

Brain Localization via Neuroimaging. Uddin and colleagues116 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.116 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.

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 impeding 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 ‘naive realism’, when individuals assume that others see the world the same way as they do and have difficulty acknowledging alternative viewpoints.123(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 compared 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-
Takahashi and Overton 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 Haier 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.

Brain regions putatively involved in wisdom that were not prominent in the review of intelligence and reasoning 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. 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. 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. The possible enhancement of wisdom and its specific subcomponents with aging-related cumulative life experience warrants investigation. Cross-cultural compari-
5. Studying neuropsychiatric disorders affecting wisdom: Research in naturally occurring disorders (eg, frontotemporal dementia or traumatic injuries [eg, case of Phineas Gage]) 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.

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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.

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