Decision-Making in Diabetes Mellitus Type 1

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Decreased treatment adherence in patients with diabetes mellitus type 1 (type 1 DM) may reflect impairments in decision-making and underlying associated deficits in working memory and executive functioning. Other factors, including comorbid major depression, may also interfere with decision-making. The authors sought to review the clinically relevant characteristics of decision-making in type 1 DM by surveying the literature on decision-making by patients with type 1 DM. Deficiencies in decision-making in patients with type 1 DM or their caregivers contribute to treatment nonadherence and poorer metabolic control. Animal models of type 1 DM reveal deficits in hippocampal-dependent memory tasks, which are reversible with insulin. Neurocognitive studies of patients with type 1 DM reveal lowered performance on ability to apply knowledge to solve problems in a new situation and acquired scholarly knowledge, psychomotor efficiency, cognitive flexibility, visual perception, speed of information-processing, and sustained attention. Other factors that might contribute to poor decision-making in patients with type 1 DM, include "hypoglycemia unawareness" and comorbid major depression (given its increased prevalence in type 1 DM). Future studies utilizing novel treatment strategies to help patients with type 1 DM make better decisions about their disease may improve their glycemic control and quality of life, while minimizing the impact of end-organ disease.

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Much of the burden of managing patients with diabetes mellitus type 1 (type 1 DM) rests with the patient and/or family members.[1] Decreased adherence to prescribed treatment of type 1 DM is a major challenge,[2] as such treatment nonadherence or "mismanagement" leads to increased healthcare costs, medical complications, hospitalizations, and fatal outcomes (such as diabetic ketoacidosis).[3] Given that poor decision-making may contribute to treatment nonadherence in this patient population, we reviewed previous studies scrutinizing the decision-making of patients with type 1 DM and examined how various factors, such as neurocognitive deficits, "hypoglycemia unawareness," and comorbid depression, might also contribute to impaired decision-making.

We conducted multiple MEDLINE searches for 2000–2011 using terms such as "diabetes," "type 1 diabetes," "decision-making," "problem-solving," "cognition," "depression," and "pathophysiology." We supplemented the

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online searches with manual reviews of article reference lists and selected articles for further review by author consensus.

WHAT TYPES OF DECISIONS DO PATIENTS WITH TYPE 1 DM HAVE TO MAKE?

Decision-making encompasses a complex set of processes that requires various higher-order cognitive functions through which individuals regulate their actions, thoughts, and emotions according to goals, current physiological or psychological states, and environmental conditions.[4] Patients with type 1 DM face a relentlessly changing environment that requires executive functioning and working memory. Executive functioning consists of an array of cognitive functions, including attention, problem-solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, initiation, and monitoring of actions.[5] Working memory, another of the "executive functions" is the ability of an individual to actively hold and manipulate information.[6] Related concepts are those of health literacy (e.g., the ability to complete basic reading required to treat their illness),[7] and health numeracy, defined as the skills needed to comprehend and use quantitative health information such as rudimentary mathematical skills (e.g., to calculate amounts of insulin and judge carbohydrate content of foods),[8] the ability to use non-text formats, such as graphs, and the capacity for oral communication.[9]

In persons with type 1 DM, salient decisions in diabetes management revolve around pre-meal insulin administration, and require an extensive collection of cognitive skills. Strategic dosing of pre-meal insulin depends on several factors (e.g., visual processing of blood glucose reading, estimation of anticipated meal size, accurate recollection of antecedent activity level, memory about experiences under similar conditions).[10] The timing of pre-meal insulin injections or boluses is related to the level of a person's pre-meal glycemia. When blood glucose levels are above a patient's desired target, increasing the time between insulin administration and meal consumption will enable the insulin to take effect. Conversely, if pre-meal blood glucose levels are under a patient's target range, administration of insulin should be delayed until just before eating.[10] Timing of pre-meal insulin injections is of great consequence for parents of young children with type 1 DM, as they must balance the benefit of pre-meal insulin administration with the possibility that the child may decide not to eat, and thereby suffer a hypoglycemic episode.

NEUROCOGNITIVE DEFICITS IN EXECUTIVE FUNCTIONING AND PROBLEM-SOLVING SKILLS THAT LEAD TO POOR GLYCEMIC CONTROL

Proper neurotransmitter function is critically important for decision-making; unpredictable levels of glucose (both high and low) in patients with poorly-controlled diabetes may deteriorate neurotransmitter functioning and contribute to cognitive dysfunction.[11] Of note is the idea that decisions to be made in situations of uncertainty (which require risk-taking and exploratory choices) involve norepinephrine in the orbitofrontal cortex, whereas predictable environments may lead to consideration of longer-delayed rewards, dependent upon serotonin in the dorsal prefrontal cortex and dorsal striatum.[12] Also, expectation of a high reward may trigger an individual's choosing an action disregarding a large risk, a decision that is influenced, in part, by dopamine in the anterior cingulate cortex.[12] Laboratory studies of animals indicate that not only turnover rate, but also steady-state level of monoamines may be altered in the brains of animals with diabetes.[13] Alloxan (45 mg/kg) diabetic rats untreated for 30 days and showing hyperglycemia (>250 mg%) had significant increases of 5-HT level in the striatum, midbrain, pons medulla, cerebellum, and cerebral cortex and elevated 5-HIAA levels in the striatum, hippocampus, and midbrain. Enhancement of biosynthesis and/or decline in metabolism rates could explain these rises in levels of 5-HT and 5-HIAA.[13]

Experiments performed with streptozotocin-induced type 1 DM rats 30 days after injection (when diabetes was well stabilized and streptozotocin was washed away) showed biochemical changes in central and peripheral catecholaminergic systems.[14] Dopamine content was reduced in the nigrostriatal system (both in the midbrain, where neuronal bodies are present, and in the synaptic terminals of the striatum). Alterations of norepinephrine occurred in the sympathetic nervous system (but not the CNS), with increases in the cardiac ventricles and decreases in the stellate ganglia and the blood serum; reduced norepinephrine synthesis and increased storage due to a reduced release from synaptic vesicles may explain these findings.[14]

Exogenously-administered insulin may lead to a reduction of monoamine turnover during hyperglycemia

and an increase during hypoglycemia.[15] Furthermore, in the setting of hyperglycemia and ischemia, the accretion of the excitatory neurotransmitter glutamate can cause CNS damage.[16]

In children with type 1 DM, the patient and his or her family must organize several critical daily management tasks (including dietary intake, exercise, blood glucose monitoring, and insulin administration).[5] In one study, 235 children with type 1 DM (mean age: 10.5 [SD: 1] years; 108 boys and 127 girls) and their primary caregivers were separately administered the Diabetes Self-Management Profile to assess treatment adherence.[5] The executive functioning of the children was measured with the Behavior Rating Inventory of Executive Functioning, and their glycemic control was assessed by HbA1c levels. The researchers found that executive functioning (e.g., planning, problem-solving, organization, working memory) was associated with adherence, which, in turn, was related to diabetes control. In fact, structural-equation modeling showed that adherence mediated the relationship between executive functioning and glycemic control.[5]

Problem-solving is an element of executive functioning that involves analysis of the problem, generation of possible solutions, evaluation of the risk/benefit profile of those solutions, and outcome analysis.[17] Cross-sectional studies of adults with type 1 DM consistently demonstrate that ineffective/poor problem-solving ability is associated with poorer glycemic control.[18] A recent study showed that children and adolescents with type 1 DM whose caregivers lack sufficient skill for responding to, and managing, blood glucose fluctuations may be at special risk for poor diabetes-related outcomes.[17] Diabetes Problem Solving Interview (DPSI) data and measures of diabetes management were obtained at baseline from 114 youths (ages 9–14.5) and 109 caregivers. Glycosylated hemoglobin (HbA1c) was measured quarterly over 9 months. For caregivers, but not youths, low DPSI scores (indicating poor problem-solving skills) were significantly associated with worse HbA1c over 9 months.[17]

Decision-making competence is the ability or capacity to form flexible and effective plans for managing different situations in the midst of pursuing personal goals.[19,20] One study[21] examined decision-making competence in a sample of adolescents (34 boys and 29 girls) between the ages of 11 and 17 years (mean age: 13.3 [SD: 1.77) years, with type 1 DM, using the Melbourne Decision-Making Questionnaire (MDMQ).[22] The MDMQ has 22 items that measure both competent (e.g., "I like to consider all the alternatives.") and maladaptive decision-making (hypervigilant, buck-passing, and procrastination). Hypervigilant decision-making is characterized by the frantic search for a way out of dilemmas and impulsively choosing hastily contrived solutions that seem to promise immediate relief.[22] Emotional excitement, perseveration, and limited attention cause the hypervigilant decision-maker to overlook the full range of consequences of choice. Higher levels of adolescent hypervigilance were associated with lower parent report of adherence ($r = -0.33$; $p < 0.01$).[21] The authors noted that the questionnaires such as the MDMQ may not reflect the processes involved in diabetes-related decisions, as diabetes-related decisions must be made on a daily basis, carry additional emotional significance, and may have short- and long-term health consequences. Relevant in this regard is that adolescents may possess competent decision-making skills in peer relationships and academics, but not about type 1 DM care, possibly explaining why this study did not demonstrate an association between adolescent decision-making competence and HbA1c values. Indeed, the treatment adherence of the parents was not measured, thereby potentially counteracting the detrimental effect of adolescent hypervigilance upon glucose control.

NEUROCOGNITIVE DEFICITS AND PATHOPHYSIOLOGIC CHANGES IN THE BRAIN: SUBSTRATES FOR IMPAIRED DECISION-MAKING IN PATIENTS WITH TYPE 1 DM

Cognitive impairment may also contribute to impaired decision-making in patients with type 1 DM. Mice with streptozotocin-induced diabetes exhibit significant memory retention deficits on hippocampus-dependent, active avoidance tasks, and deficits in performance on spatial learning and memory tasks that worsened with task complexity.[23] Hyperglycemia also appears to exert a deleterious effect on the hippocampal neurons (and their neuroplasticity) of rats, causing decreased long-term potentiation (i.e., decreased sprouting), which is related to the degree of hyperglycemia.[24] Fortunately, sprouting improved with glycemic control.[25] Moreover, in animal models, administration of exogenous insulin improves performance on some learning tasks and corrects the learning and memory deficits associated with streptozotocin-induced diabetes. That is, insulin

treatment reverses deficits in hippocampus-dependent, active avoidance tasks in streptozotocin-treated diabetic rats,[26] and prevents streptozotocin-induced impairments in water-maze learning (and hippocampal long-term potentiation).[27]

Whether peripheral insulin is able to traverse the blood–brain barrier to act upon CNS insulin receptors remains an unresolved and controversial issue. Insulin receptors are densely expressed in the hippocampus, and brain insulin receptors may simply be activated by intrinsic CNS or insulin-related molecules.[28] Thus, these preclinical models of type 1 DM have revealed cognitive deficits in memory that likely represent in humans a specific abnormality in hippocampus-dependent declarative memory,[29] and insulin is thought to act at this brain structure to facilitate learning and memory.[30]

In a metaanalysis of 33 studies on cognitive performance in patients with type 1 DM, Brands and coworkers documented a significantly lowered performance on ability to apply knowledge to solve problems in a new situation and also on acquired scholarly knowledge ($d = -0.7$; moderate effect size), psychomotor efficiency ($d = -0.6$), cognitive flexibility ($d = -0.5$), visual perception ($d = -0.4$), speed of information-processing ($d = -0.3$, mild effect size), and sustained attention ($d = -0.3$).[31] Perhaps not surprisingly, lowered cognitive performance was associated with presence of microvascular complications (e.g., retinopathy, nephropathy).

Interestingly, the cross-sectional studies [32–38] included in the metaanalysis revealed no consistent relationship between disease duration and cognition, perhaps, at least in part, because persons may differ in terms of the magnitude of their diabetes (dys)control.[31] Nevertheless, as the duration of type 1 DM increases, development of diffuse brain degeneration, demyelination of cranial nerves and spinal cord, and nerve fibrosis and pseudocalcinosis within the CNS may ultimately impair cognition and decision-making.[11] Imaging studies of brains of patients with type 1 DM have revealed white-matter microstructural deficits, cerebral atrophy, increases in regional cerebral blood flow, leukoaraiosis (periventricular white-matter disease), lower gray-matter density, and reductions in hippocampal and amygdalar volume.[39] These structural changes may contribute to consequent impairment of decision-making.

One study used blood oxygen level-dependent (BOLD) functional magnetic resonance imaging during euglycemic (5.0 mmol/L) and hypoglycemic (2.8 mmol/L) hyperinsulinemic clamps to investigate the effects of acute hypoglycemia on working memory and brain functioning in patients with Type 1 DM.[40] The experiment compared brain activation response to a working-memory task (WMT) in subjects with type 1 DM (N=16) to that of age-matched non-diabetic control subjects (N=16). BOLD activation was increased and deactivation was decreased in type 1 DM versus control subjects, which indicates that subjects with type 1 DM have reduced cerebral efficiency (i.e., they require a higher level of brain activation to achieve the same level of cognitive performance as control subjects).[40] Thus, taken together, decreased treatment adherence of patients with type 1 DM may result from impairments in decision-making and underlying deficits in working memory and executive functioning.

MISINTERPRETATION OF SOMATIC CLUES AND "HYPOGLYCEMIA UNAWARENESS" MAY CONTRIBUTE TO POOR DECISION-MAKING IN TYPE 1 DIABETES

Patients with type 1 DM often depend on "body listening" to pick up bodily cues indicative of hypo- or hyperglycemia.[41] Atypical somatic cues of hypoglycemia and hyperglycemia for some patients may involve changes in the taste of saliva, mood alterations, changes in the taste of water, alterations in libido, changes in energy levels, dryness in the mouth, visual changes, or a change in the sensation of lips or tongue.[42] In order to manipulate exogenous factors (such as insulin, dietary choices, and physical activity levels), patients with type 1 DM need to know what their blood glucose is and in which direction it is going.[43] For instance, a blood glucose level of 60 mg/dl that is rising may need no intervention, whereas a level of 65 mg/dl that is failing may require immediate consumption of fast-acting carbohydrates. Although type 1 DM patients clearly became symptomatic during hypoglycemia, pattern of symptoms vary widely; and studies of adults (ages 18–44)[44] and adolescents (ages 11–19)[45] have shown that most patients are unable to accurately estimate their blood glucose level.[44] Potential explanation for their misinterpretation is that patients monitor symptoms that do not accurately discriminate between hyperglycemia and hypoglycemia, or "feel" certain symptoms of a blood glucose fluctuation, but inaccurately interpret them.

Thus, the "somatic marker hypothesis," as proposed by Bechara and colleagues,[46] may be especially salient to

conceptualize decision-making in patients with type 1 DM. This hypothesis holds that decision-making is a process guided by emotions and that overt reasoning is preceded by a nonconscious biasing step. This process employs neural systems (such as those regulating homeostasis, emotion, and feeling),[46] other than those that support declarative knowledge.[47] Anticipatory skin-conductance responses, an autonomic "somatic marker" of feelings generated by secondary emotions, may occur during decision-making tasks such as the Iowa Gambling Task.[48] According to the "somatic marker hypothesis," decision-making is a process influenced by marker signals (e.g., "gut feeling" or "hunch") regarding the internal milieu, and a defect in emotion and feeling interferes with decision-making.[49] Emotions rely on the limbic system, which includes brainstem reward-processing structures (e.g., ventral tegmental area), areas of the midbrain and cortex to which they project (e.g., nucleus accumbens and ventromedial frontal, orbitofrontal, and anterior cingulate cortex), and other areas such as the insular cortex and amygdala.[50]

In addition to misinterpretation of somatic cues, "hypoglycemia unawareness" may also contribute to poor decision-making in patients with type 1 DM. Episodes of hypoglycemia cause "hypoglycemia unawareness" (by lessening sympatho-adrenal and associated neurogenic symptoms to a certain level of subsequent hypoglycemia), defective glucose counter-regulation (via lowering epinephrine responses to a given level of subsequent hypoglycemia in the setting of absent decrements in insulin and absent increments in glucagon), and a lowered hypoglycemic threshold for hypoglycemic symptoms. [51–54] These factors further increase the risk of severe hypoglycemia during insulin therapy of type 1 DM.[55]

Cerebral neuronal activation increases during symptomatic hypoglycemia, and, in "hypoglycemia unawareness," this activation is reduced.[56] Habituation (desensitization of physiologic response to stressor)[57] to recurrent hypoglycemia involves differential involvement of cortical mechanisms involved in learning and conditioning (rather than, or in addition to, hypothalamic glucose-setting alterations).[55] The pattern of decreased activation in stress pathways (e.g., amygdala and hypothalamus) and intact activation of brain regional networks subserving hedonic responses (e.g., motivation [ventral striatum] and reward-perception [lateral orbitofrontal cortex]) seen in the unaware subjects (as compared with aware subjects) suggests that the experience of hypoglycemia may be not just subjectively neutral but, instead, subjectively rewarding to the person. This phenomenon has implications for decision-making, as evidenced by a study showing that patients with hypoglycemia-unawareness were significantly less adherent to agreed-upon changes to insulin regimens designed to avoid hypoglycemia (hypoglycemia-awareness can be restored by hypoglycemia-avoidance) than their hypoglycemia-aware counterparts, despite increased clinical contact.[58] These findings are compatible with habituation to hypoglycemic stress. Notably, this failure to perceive a situation (e.g., hypoglycemia) as dangerous undermines motivation, ability to change behavior, and, ultimately, treatment adherence.[59] The authors suggest that behavioral strategies addressing habituation may help restore hypoglycemia-awareness and protect against severe hypoglycemia.

One study of cognitive functioning before, during, and after hypoglycemia in two groups of adult type 1 diabetic patients (ages 18–45), 20 with normal hypoglycemia awareness (NHA) and 16 with impaired hypoglycemia awareness (IHA) revealed that performance in the NHA group was impaired on cognitive tasks of the four-choice reaction-time test, Digit Symbol Substitution Task, and Trail-Making B test during hypoglycemia (and remained impaired for up to 75 minutes on the four-choice reaction-time test).[60] Remarkably, cognitive performance did not deteriorate significantly during hypoglycemia in the IHA group (with the exception of the Digit Symbol Substitution Task after 60 minutes of hypoglycemia). Adaptation to low blood glucose had apparently occurred in the IHA patients, as shown by preservation of their cognitive functioning at a blood glucose level of 2.5 mmol/l. The IHA group had a longer duration of diabetes (median: 33.5 years [range: 22–43]) than the NHA group (29 [19–44] years; $p < 0.001$). The IHA group also evidenced a higher prevalence of microvascular complications (six patients in the IHA group and one patient in the NHA group; $\chi^2 = 5.994$; $p = 0.013$). Comparisons of gender, age, A1c, and BMI were nonsignificant. In this study, IHA was associated with "protection" against cognitive dysfunction during hypoglycemia.[61] These individuals did not show the cognitive dysfunction of the NHA patients, which potentially serves as a warning signal (somatic marker) of impending danger, allowing NHA patients the opportunity to decide to take action to increase their blood glucose.

Fortunately, if patients can adhere to programs consisting of strict monitoring to avoid even mild hypoglycemia

TABLE 1. Comorbid Depression May Contribute to Impaired Decision-Making in Patients With Type 1 Diabetes Mellitus

Increased everyday decisional conflict and rumination, low self-efficacy, and lack of concentration may lead to poor adaptation to Type 1 DM and its variations over time.
Inward focus may impair ability to engage in collaborative/alliance work with family members and healthcare providers.
Limited ability to shift behavior under changing contingencies and altered reward-processing, which may involve an inflexible, generalized response to reward.
Impaired risk-related behavior can have potentially serious short- and long-term consequences.
Disruption of limbic-cortical pathways in depressive illness causes alteration of feeling and emotion, and consequently may lead to poor decision-making in patients with depressive illness. Comorbid depressive disorders may contribute to cognitive deficits in patients with Type 1 DM through alterations in these limbic-cortical networks.

episodes, blunted counterregulatory hormonal responses and autonomic symptoms improve.[62] Also, psychosocial interventions may help with these problems in body awareness. For instance, Blood Glucose Awareness Training (BGAT), an 8-week psychoeducational training program, has been shown to improve an individual's ability to detect, anticipate, avoid, and treat extremes in blood glucose levels.[43] More recently, 4 weeks of real-time continuous glucose monitoring (CGM) with preset alarms at specific glucose levels have been a useful tool to achieve avoidance of hypoglycemia in adolescents with type 1 DM with hypoglycemia unawareness, and it improved their counterregulatory response to hypoglycemia (as measured by epinephrine response during hyperinsulinemic hypoglycemic clamp studies) as compared with adolescents with type 1 DM with hypoglycemia-unawareness in the standard therapy group.[63]

COMORBID DEPRESSION MAY CONTRIBUTE TO DECISION-MAKING IMPAIRMENTS IN PATIENTS WITH TYPE 1 DM

Patients with type 1 DM and comorbid depression may plausibly suffer from poor decision-making (Table 1). Accumulating evidence suggests that adults with type 1 DM are at least twice as likely as non-diabetic individuals to exhibit clinically significant depression.[64] Indeed, the Coronary Artery Calcification in Type 1 Diabetes Study, which showed that the 458 participants with Type 1 DM (47% male, age 44 [SD: 9] years, Type 1 DM duration 29 [SD: 9] years) exhibit a prevalence rate of depression of 17.5%, versus the prevalence rate of 5.7% of 546 non-diabetic, age- and gender-matched control subjects (51% male, age 47 [SD: 9] years; $p < 0.0001$),[65] as assessed by Beck Depression Inventory (BDI-II)[66] score >14. Also, more participants with type 1 DM were classified as depressed than those in the control group when the definition included current antidepressant use or BDI-II score >14 (32% versus 16%; $p < 0.0001$). Furthermore, those type 1 DM participants with at least one diabetes complication (retinopathy, blindness, neuropathy, diabetes-related amputation, and kidney or pancreas transplantation; N=209) scored significantly higher on the BDI-II (mean BDI-II score: 10.7 [SD: 9.3]) than participants with type 1 DM without complications (mean BDI-II score: 6.4 [SD: 6.3]; $p < 0.0001$). The cause–effect relationship could not be determined because of the cross-sectional nature of this study.[65]

The ruminative, perseverant thoughts characteristic of depressive illness may impair the ability of patients with type 1 DM to balance everyday responsibilities with the prioritization of personal tasks critical to maintaining their physical health.[67] A study of decision-making in depressed patients (without type 1 DM) used a one-item self-report measure to assess decisional conflict ("Do you feel conflicted when you have to make a decision?") and a 20-item questionnaire for measuring ongoing processes during decision-making (Processes of a Decision-Making Questionnaire).[67] The results showed that depressed patients experience increased levels of day-to-day decisional conflict (the aversive experience that accompanies indecisiveness), when compared with patients without depression. Furthermore, depressed patients often suffer from a lack of concentration, low self-efficacy, and rumination. Depressed individuals focus their attention inward and evaluate their competence, whereas healthy individuals focus upon the task. The inward focus of these depressed patients may hamper their collaboration with potentially helpful family members and accessing resources of healthcare providers.[41]

Decision-making is a higher-order cognitive function that involves the ability to choose between competing actions that are associated with varying levels of risk

TABLE 2. Frequent Paradigms Used to Study Decision-Making

Paradigm	Description	Neuropsychological Target
Iowa Gambling Task (IGT)	Selection of cards of four different stacks, with different monetary gains and penalties	Risk and reward processing
Modified IGT (contingency-shift)	A two-phase IGT in which the reward/risk characteristics of the decks are systematically changed	Set-shifting as a measure of flexibility and adaptability
Cambridge Gambling Task[79]	Probabilistic choice of finding a hidden token behind 10 boxes	Risk-assessment without learning confounds
Wheel of Fortune	Two-choice task with probabilistic monetary outcomes	Separately targets reward and punishment processing

and reward.[68] Reward-related decision-making was examined within a longitudinal study of 221 11-year-old boys, 25 of whom had a depressive disorder at age 10 or 11.[69] Participants completed a behavioral decision-making task called the reward-contingent decision (RCD) paradigm [70,71] (see Table 2) which involves reward-related decisions under conditions of uncertainty and is considered to be emotional in nature. Boys with depression failed to distinguish between options involving small or large possible reward under conditions involving a high probability of winning. The results indicate that depression might involve a rigid, generalized strategy for responding to reward and limited ability to shift behavior under changing contingencies. Impaired flexible decision-making has also been demonstrated in adults with major depressive disorder (MDD) (N=19, mean age: 35.8 [SD: 10.1]) as compared with healthy controls (N=20; mean age: 35.1 [SD: 9.3])[72] during the standard Iowa Gambling Test (IGT)[73] and the contingency-shifting variant, IGT.[74,75] Analysis of the contingency-shift phase demonstrated that individuals with depression had difficulties determining when a previously bad contingency became favorable. Mental inflexibility in patients with type 1 DM and comorbid depression may impair their ability to vary strategies for changing conditions and thereby contribute to dangerous fluctuations in blood glucose.

One functional MRI study investigated how neural correlates of reward-related decision-making in young people (ages 9–17) with MDD differ from those in typically-developing control children.[76] The reward task (adapted from Rogers et al.)[71] involves choices about possible rewards involving varying magnitude and probability of reward; group differences in two reward processes, decision-making/anticipation and outcome, were examined. In the decision phase, those with depression exhibited a pattern consistent with decreased emotional reactivity to reward: blunted responses in the anterior cingulate cortex (ACC), bilateral caudate, and inferior orbitofrontal cortex (OFC) bilaterally, especially during high-magnitude reward conditions. The participants with depression also exhibited increased response in the middle and superior OFC bilaterally (especially to low-magnitude reward), a pattern consistent with over-regulation. Depression is also associated with generally diminished responses, particularly in conditions of small-magnitude reward, as evidenced by blunted response in the ACC, caudate, and OFC (particularly during loss and low-magnitude reward, but increased response in the amygdala). After high-magnitude rewards, those with depression exhibited a greater response than control participants in the amygdala bilaterally and the inferior OFC.[76]

In another neuroimaging study using fMRI,[68] 22 adolescents with no personal or family history of psychiatric illness and 22 adolescents with MDD were administered a two-choice decision-making task involving probabilistic monetary rewards with varying levels of risk: the Wheel of Fortune.[77] During risky decision-making, healthy adolescents used the brain regions involved in inhibitory control (right lateral OFC), whereas depressed adolescents engaged areas involved in conflict monitoring (right caudal ACC). The authors hypothesized that reduced inhibitory control, as reflected by reduced activation of the right lateral OFC in depressed adolescents, may provide a neurobiological explanation for impulsivity (e.g., suicidal behavior and substance abuse among depressed youth).[68]

Because patients with type 1 DM exhibit an increased prevalence of depressive symptoms, and, as decision-making is impaired in patients with major depressive disorder (MDD), the "somatic marker hypothesis"[46] may be especially relevant in conceptualizing decision-making in patients with type 1 DM and comorbid MDD. Mayberg has proposed a working model of depression, implicating failure of the coordinated interactions of

a distributed network of limbic–cortical pathways.[78] Disruption of limbic–cortical pathways in depressive illness causes alteration of feeling and emotion, and consequently may lead to poor-decision making in patients with depressive illness. Comorbid depressive disorders may contribute to cognitive deficits in patients with Type 1 DM through alterations in these limbic–cortical networks via perturbations in insulin-glucose homeostasis, adipokine synthesis and secretion, intracellular signaling cascades, mitochondrial respiration (reactive oxygen species), and immuno-inflammatory processes (proinflammatory cytokines, acute phase reactants, and cellular adhesion molecules).[28]

Despite the multiple areas in which decision-making is impaired in patients with major depressive disorder (MDD), no studies have utilized sophisticated, "in-the-laboratory" decision testing (Table 2) of patients with type 1 DM and comorbid depression to compare them to non-depressed patients with type 1 DM. The extent to which impaired decision-making contributes to the poorer outcome of patients with type 1 DM and comorbid depression remains to be determined.

CONCLUSIONS AND FUTURE DIRECTIONS

A small extant literature documents that those patients with type 1 DM suffer neurocognitive deficits of executive functioning and working memory, which is associated with poorer glycemic control. Other contributors to poor decision-making in type 1 DM likely include neurocognitive deficits, "hypoglycemia unawareness," and comorbid depression. The overlapping fields of neurocognitive psychology, endocrinology, and affective-disorders research can now sustain integrative research for screening of patients with type 1 DM for deficits in cognitive dysfunction and decision-making, discerning the impact of comorbid depressed mood, and whether treatment to improve decision-making in patients with type 1 DM will improve both glycemic and mood outcomes. Cross-sectional studies can be performed to measure the impact of brain glucose levels (e.g., with a glucose clamp) upon decision-making (e.g., using the Iowa Gambling task). Longitudinal studies will further clarify the impact of poor decision-making on diabetes outcomes, and, conversely, the contribution of duration and severity of type 1 DM upon one's decision-making capacity. State-of-the-art functional neuroimaging can further reveal the underlying neuronal networks whereby hypoglycemia (or hyperglycemia) impairs decision-making in patients with type 1 DM, without and with comorbid depressed mood. This new knowledge, will help develop novel treatment strategies to help these patients make better decisions about their disease, thereby improving their glycemic control and quality of life, while minimizing the impact of end-organ disease.

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