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Invited review

Cognitive dysfunction and metabolic comorbidities in mood disorders: A repurposing opportunity for glucagon-like peptide 1 receptor agonists?

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ABSTRACT

Major depressive disorder and bipolar disorder are highly prevalent and disabling conditions. Cognition is considered a core domain of their psychopathology and a principle mediator of psychosocial impairment, disproportionately accounting for overall illness-associated costs. There are few interventions with replicated evidence of efficacy in treating cognitive deficits in mood disorders. Evidence also indicates that cognitive deficits are associated with obesity and involve significant impairment across multiple domains. Conversely, weight-loss interventions, such as physical exercise and bariatric surgery, have been shown to beneficially affect cognitive function. This convergent phenomenology suggests that currently available agents that target metabolic systems may also be capable of mitigating deficits in cognitive functions, and are, therefore, candidates for repurposing. The incretin glucagon-like peptide-1 (GLP-1) is a hormone secreted by intestinal epithelial cells. GLP-1 receptors (GLP-1R) are widely expressed in the central nervous system. Activation of GLP-1R leads to facilitation of glucose utilization and antiapoptotic effects in various organs. Pre-clinical trials have demonstrated significant neuroprotective effects of GLP-1, including protection from cell death, promotion of neuronal differentiation and proliferation; and facilitation of long-term potentiation. Liraglutide is a GLP-1R agonist that has been approved for the treatment of type 2 diabetes mellitus and obesity. Convergent preclinical and clinical evidence, including a proof-of-concept pilot study from group, has suggested that liraglutide may improve objective measures of cognitive function in adults with mood disorders. The safety and availability of GLP-1R agonists indicate that they are promising candidates for repurposing, and that they may be viable therapeutic options for mood disorders.

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Contents

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1. Introduction

Mood disorders (i.e. major depressive disorder [MDD] and bipolar disorder [BD]) and metabolic disorders (e.g. type 2 diabetes mellitus [T2DM], obesity, metabolic syndrome) are amongst the major causes of disability and mortality worldwide. Individually, these conditions are responsible for high levels of chronic disability and healthcare-related costs (Mathers et al., 2006; Vos et al., 2012; Whiteford et al., 2013); however, their co-occurrence represents a particular challenge for patients, families, providers and healthcare systems (O'Neil et al., 2013; Comino et al., 2015; Liu et al., 2017). Meta-analytic studies have documented that individuals with mood disorders have an approximately 2-fold increased risk of T2DM, relative to the general population (Vancampfort et al., 2015a). It is estimated that the prevalence of T2DM in individuals with mood disorders is between 8 and 10% (Vancampfort et al., 2015a, 2015b), whereas the prevalence of metabolic syndrome is approximately 30% (Vancampfort et al., 2015c). As a result, mood disorders are associated with excessive and premature mortality, mainly driven by cardiovascular disease and/or diabetes complications (Westman et al., 2013; Kessing et al., 2015; Osby et al., 2016). It is estimated that individuals with mood disorders have a reduced life expectancy of between 10 and 15 years, the majority of it, even for adolescents and young adults, accounted by natural causes (Kessing et al., 2015; Laursen et al., 2016).

Convergent lines of inquiry also indicate that the mood-metabolic disorders association is bidirectional (Luppino et al., 2010; Pan et al., 2012; Mannan et al., 2016). For example, it is reported that adults with T2DM have an approximate 2–3 fold greater risk for subsequently declaring MDD or BD Wahlqvist et al., 2012. The co-occurrence of metabolic and mood disorders is associated with a more complex illness presentation. Individuals with a mood disorder and comorbid obesity, insulin resistance (IR) or T2DM have an unfavorable course of mood disorders, characterized by an overrepresentation of atypical features, a predominance of chronic/persistent trajectories, higher risk of suicide, treatment resistance and functional disability (Calkin et al., 2015; Ruzickova et al., 2003; Goldstein et al., 2013; Mansur et al., 2016; Handley et al., 2015; Shapiro et al., 2016). In T2DM cohorts, the presence of mood syndromes and/or symptoms has been associated with elevated incidence of complications and all-cause mortality (Nefs et al., 2012, 2016).

Identifying novel treatments for mood disorders remains a pressing need as approved evidence based treatment options are limited. Although most individuals with MDD respond to pharmacological and/or psychosocial treatments, the majority of the patients do not achieve remission (Jakobsen et al., 2011; Cuijpers et al., 2011; Casacalenda et al., 2002; Rocha et al., 2012), and approximately 80% of the patients experience at least 1 more episode after their first episode of depression (Fava et al., 2006; Steinert et al., 2014). Limited efficacy of the available therapeutic options, characterized by a low rate of recovery and a high rate of recurrence, was also reported in BDJudd et al., 2005; Geddes and Miklowitz, 2013. In addition, there are insufficient empirically supported interventions to prevent, manage or mitigate the detrimental effects of metabolic comorbidities in the mood disorders population. Underscoring the lack of progress in this area is data from epidemiological studies, which have documented that the aforementioned gap in life expectancy between individuals with a mood disorders and the general population has increased in the past decades (Osby et al., 2016; Lawrence et al., 2013).

2. Cognition, metabolism and mood disorders

Cognition is considered a core dimension/domain of psychopathology in both MDD and BDSnyder, 2013; Bourne et al., 2013; Mann-Wrobel et al., 2011; Lee et al., 2012. Cognitive dysfunction has been consistently demonstrated across multiple studies and approximately 25–50% of patients exhibit pronounced deficits (defined as more than 1 or 2 standard deviations below the mean on at least one cognitive domain) (Gualtieri and Morgan, 2008; Martino et al., 2008). Notably, cognitive deficits in mood disorders have been found to be a principal mediator of psychosocial impairment and disability, independently of concurrent mood symptoms (Depp et al., 2012; Iosifescu, 2012; McIntyre et al., 2013a; Andreou and Bozikas, 2013), and to disproportionately account for overall illness-associated costs (Greenberg et al., 2003; Kessler et al., 2008; Kleine-Budde et al., 2014). Currently approved treatments for mood disorders (e.g. antidepressants, mood stabilizers, antipsychotics) have been shown to be mostly ineffective at treating cognitive impairment, and, as a result, recovery from mood symptoms is often not accompanied by improvement in cognitive symptoms (McIntyre et al., 2013a; Dias et al., 2012; Trivedi and Greer, 2014; Rosenblat et al., 2016).

Although evidence indicates that executive function impairment is an independent feature of mood disorders, several moderators have been reported, such as socio-demographic and clinical features (Snyder, 2013; Bourne et al., 2013; Mann-Wrobel et al., 2011; Lee et al., 2012; McIntyre et al., 2013a). More recently, the moderational effect of metabolic comorbidities has been increasingly reported (Bove et al., 2013; Gluck et al., 2013; Kenna et al., 2013; Karlamangla et al., 2014; Nazaribadie et al., 2014; Samaras et al., 2014; Sanz et al., 2013; Sun et al., 2014; Yogi-Morren et al., 2014; Geijselaers et al., 2014). Multiple metabolic abnormalities are independently associated with poor executive function. Studies with clinical and healthy control populations have shown that impaired glucose metabolism and insulin resistance (Gluck et al., 2013; Kenna et al., 2013; Nazaribadie et al., 2014; Samaras et al., 2014; Sanz et al., 2013; Yogi-Morren et al., 2014; Geijselaers et al., 2014), visceral adiposity (Bove et al., 2013; Sanz et al., 2013), dyslipidemia (Karlamangla et al., 2014; Yogi-Morren et al., 2014) and high blood pressure (Karlamangla et al., 2014; Sun et al., 2014) are independently associated with impaired executive function. Overweight/obesity, metabolic syndrome and T2DM have all been consistently shown to negatively impact a variety of cognitive domains (Gunstad et al., 2007, 2010; Taylor and MacQueen, 2007; McCrimmon et al., 2012; Vincent and Hall, 2015).

Convergent evidence also indicates that, within individuals with a mood disorder, neurocognitive dysfunction is more impaired in overweight/obese individuals, when compared to normal weight patients (McIntyre et al., 2013a; Watari et al., 2006; Yim et al., 2012; Depp et al., 2014; Restivo et al., 2017). A recent offspring study documented that at-risk individuals (i.e. defined as having a first-degree relative with BD and concurrent symptoms) were more likely to display cognitive dysfunction as a function of increasing overweight status (McIntyre et al., 2017). Moreover, a detrimental

effect of metabolic comorbidities on cognitive function is also reported in individuals with schizophrenia (Lindenmayer et al., 2012; Takayanagi et al., 2012; Guo et al., 2013). Overall, cognitive function has been a domain of psychopathology consistently associated with metabolic dysfunction.

Cognitive dysfunction is thought to be subserved by abnormalities in distributed brain circuits (Snyder, 2013; Collette et al., 2006; Niendam et al., 2012). Evidence suggests that, in mood disorders, mechanisms of neural plasticity and cellular resilience underlie the dysregulation in brain circuits (McIntyre et al., 2013a; Strakowski et al., 2012). Accumulating evidence indicate that alterations in metabolic pathways may be relevant to neurocognitive decline in subpopulations of individuals with BD and MDD. Hyperglycemia and hyperinsulinemia have been reported to influence pathways involved in neuroplasticity (Trudeau et al., 2004; Bosco et al., 2011). Imbalances in regulatory neurohormonal and related systems (i.e., pro-oxidant/anti-oxidant system, immune-inflammatory pathways and glucocorticoids function and activity) may alter pro-apoptotic intracellular signaling cascades thereby resulting in neuronal/glial loss and neurocognitive decline (McIntyre et al., 2008, 2013a; Maritim et al., 2003; Reagan, 2012; Tran et al., 2012; Karunakaran and Park, 2013). Conversely, multiple studies indicate that global disorders of metabolism (i.e. T2DM and obesity) can affect brain structure and function. Neuroimaging and neurophysiology studies of T2DM have demonstrated widespread patterns of white matter abnormalities in discrete pathways (Kodl et al., 2008; Hsu et al., 2012; van Duinkerken et al., 2012a; Reijmer et al., 2013a; Reijmer et al., 2013b), and alterations in functional connectivity (Cooray et al., 2011; Musen et al., 2012; van Duinkerken et al., 2012b). Moreover, insulin resistance in non-diabetic populations has been associated with lower hippocampal volume and altered default mode network activity (Kenna et al., 2013; Rasgon et al., 2011). Obesity has also been associated with functional abnormalities in several regions, including temporal lobe and fronto-occipital networks and the default mode network (Garcia-Garcia et al., 2012; Kullmann et al., 2012).

In summary, cognitive function is considered a core feature of mood disorders psychopathology and a leading cause of morbidity. To date, no interventions have been demonstrated to be reliably and robustly effective for the cognitive deficits of mood disorders. Treatment development has been hindered about the lack of information regarding the mechanistic pathological processes that contribute to abnormalities in the neural substrates subserving cognitive function. Available evidence indicates that metabolic disorders result in alterations in the structure, function, and neurochemical composition of the CNS regions/structures that are convergent with structures implicated in the cognitive dysfunction observed in normal weight adults with mood disorders. The foregoing collections of observations provide the basis for hypothesizing that interventions capable of mitigating molecular targets relevant to primary metabolic disorders may have a repurposing opportunity in positively affecting CNS structures implicated as subserving cognitive functions in adults with mood disorders.

3. Glucagon-like Peptide-1 (GLP-1) and cognitive function

Incretins are endogenous hormones synthesized and secreted by intestinal L-cells in the ileum and colon after meals. Several endogenous incretins have been identified, including, but not limited to, glucagon like peptide 1 (GLP-1). Activation of GLP-1 receptors (GLP-1R) leads to facilitation of glucose utilization and anti-apoptotic effects in various organs (Cabou et al., 2008; Drucker, 2003; During et al., 2003; McClean et al., 2010). Pre-clinical evidence indicates GLP-1 and its canonical receptors are identified in CNS structures and regions relevant to general cognitive processes (e.g. prefrontal cortex, hippocampus, amygdala) (Alvarez et al., 2005; Farr et al., 2016). Indeed, multiple studies have demonstrated that GLP-1 and GLP-1R agonists (e.g., exendin-4 [Ex-4], liraglutide, exenatide) are capable of crossing the blood-brain barrier (BBB) Kastin et al., 2002; Hunter and Holscher, 2012; Secher et al., 2014; Christensen et al., 2015, and act centrally to modulate food intake (D'Alessio et al., 2005), glucose homeostasis (Sandoval et al., 2008), the hypothalamic stress response (Rinaman, 1999), and regulation of blood pressure and heart rate (Yamamoto et al., 2002).

Results from preclinical studies indicate that GLP-1 agonism results in pro-cognitive effects. For example, mice injected daily for 8 weeks with liraglutide exhibited significantly enhanced learning and memory in object recognition and water maze tasks (McClean et al., 2011; Porter et al., 2010). Another study observed that mice after a single injection of GLP-1 were more capable of spontaneous alteration in the Y-maze task, suggesting that GLP-1 also improves cognitive flexibility, a component of executive function (Iwai et al., 2009). Studies that examined mice fed a high-fat diet, a model which typically results in decreased cognitive performance (Stranahan et al., 2008), documented a protective effect of GLP-1 analogues (Gault et al., 2010; Lennox et al., 2014). In keeping with these observations, GLP-1R−/− knockout mice demonstrate impaired spatial learning and memory, as shown by their worse-than-controls performance in the Morris water maze task, longer time to completion, and poorer recall of landmarks (Abbas et al., 2009). GLP-1R −/− mice did not, however, show any differences in exploratory behavior on an open field assessment task, indicating that behavior is not generally impaired, but that the impairments are specific to cognitive processes implicated in memory (Abbas et al., 2009).

3.1. Cellular effects of GLP-1R agonists

Pre-clinical evidence indicates that the potential effects of GLP-1 on cognitive function may be secondary to its effects on neuronal excitability, survival and proliferation (McIntyre et al., 2013b; Liu and Pang, 2016). Activation of GLP-1R has been shown to modulate synaptic transmission in various regions, including the mesolimbic systems and fronto-limbic pathways (Liu and Pang, 2016; Hsu et al., 2017). For example, it is reported that GLP-1 signaling regulates neurotransmitters release (e.g. glutamate, gamma-aminobutyric acid [GABA] and dopamine) in hippocampal and striatal neurons (Oka et al., 1999; Korol et al., 2015; Reddy et al., 2016; Fortin and Roitman, 2017).

Studies using in vitro cultured cells have demonstrated that pre-treating cells with GLP-1R agonists can protect them against cell death caused by amyloid beta (Aβ) plaque accumulation, a biomarker for Alzheimer's disease (AD) (Perry et al., 2003; Li et al., 2009; McClean and Holscher, 2014; Cai et al., 2014). Multiple studies administering GLP-1R agonists have since shown the potential for protecting long-term potentiation (LTP) from deficits induced by multiple agents. Administration of GLP-1 prior to Aβ treatment protected LTP from impairment in mouse models of AD (Gault and Holscher, 2008; Gengler et al., 2012; Wang et al., 2010). Liraglutide was also demonstrated to prevent synapse loss and deterioration of synaptic plasticity (McClean et al., 2011); and to rescue hippocampal LTP from deficits induced by an acute high fat diet (Porter et al., 2010; Gault et al., 2010). Most significantly, administration of liraglutide was found to rapidly facilitate LTP in healthy rats (McClean et al., 2010). In contrast, GLP-1R −/− mice had significant impairments in LTP, compared to controls (During et al., 2003; Abbas et al., 2009).

GLP-1R agonists have been implicated in the proliferation and differentiation of neural stem/progenitor cells. PC12 cell cultures treated with nerve growth factor (NGF) tend to develop

morphological characteristics similar to neurons (e.g. long and branching membranes). GLP-1 treated cells also develop neuron-like properties (Perry et al., 2002). Administration of Ex-4 increases proliferation of neural stem/progenitor cells, a process central to neurogenesis (Bertilsson et al., 2008). Progenitor cell division, important for differentiation, was enhanced in mouse models by 100–150% after injection of a GLP-1R agonist (McClean et al., 2011; Hamilton et al., 2011).

The antiapoptotic and neuroprotective effects of GLP-1 are thought to be, at least partially, mediated through improvements in the cellular metabolic milieu. Ex-4 intervention in T2DM rats was shown to prevent tau hyperphosphorylation, another pro-apoptotic marker of AD, through increased insulin signaling (Xu et al., 2015). Vildagliptin, a drug that inhibits the inactivation of GLP-1 by the enzyme dipeptidyl peptidase-4 (DPP-4), was shown to prevent neuronal insulin resistance by improving neuronal insulin receptor phosphorylation, and to improve brain mitochondrial function in rats fed a high-fat diet (Pipatpiboon et al., 2013). A study of GLP-1 treated cell cultures demonstrated that GLP-1 treatment protected neurons from apoptosis induced by methylglyoxal (MG), a marker of oxidative imbalance and a product of chronic hyperglycemia (Xu et al., 2015). In particular, one study found that GLP-1 and Ex-4 treatment protected cells from hypoxia-induced apoptosis, a protective effect that was not observed in cells cultured from GLP-1R −/− knockout mice (Li et al., 2009). Furthermore, studies have reported that liraglutide and exenatide treatment reduced inflammatory activation in a mice model of AD and cerebral ischemia (McClean and Holscher, 2014; Darsalia et al., 2012; Teramoto et al., 2011).

3.2. Central effects of GLP-1R agonists

Preliminary evidence suggests that GLP-1R agonism may result in increased activation of neural circuits in specific areas. Animal studies have reported that peripheral GLP-1 administration induced a significant increase in the neuronal activity of the hypothalamic ventromedial and paraventricular nuclei, and the parabrachial nucleus (Parkinson et al., 2009; Katsurada et al., 2014; Richard et al., 2014). A recent animal study documented that hippocampal glutamatergic neurons that provide excitatory input to the medial PFC express GLP-1R; and that its activation modulated behavior (i.e. food motivation) (Hsu et al., 2017). In humans, an increase in hypothalamic connectivity was shown 2 h after a single intravenous dose of exenatide in obese male volunteers (Schlogl et al., 2013). A separate study showed increased brain responses in reward-related brain regions (insula and amygdala) following administration of exenatide, with the effects being largely blocked by prior GLP-1R blockade (van Bloemendaal et al., 2014). Of note, GLP-1 and GLP-1R agonists effects on brain activation have been shown to be context-dependent, with evidence indicating that metabolic status (e.g. obesity vs. normal weight), metabolic mediators (e.g. glucose and leptin levels) and task (e.g. food anticipation or consumption) modulate the response of brain regions to GLP-1R activation (Farr et al., 2016; van Bloemendaal et al., 2014; Gejl et al., 2014; van Bloemendaal et al., 2015a; van Bloemendaal et al., 2015b; Heni et al., 2015).

Evidence from preclinical studies indicates that GLP-1 analogues may improve brain insulin sensitivity and glucose metabolism. Reduced levels of brain insulin resistance following administration of GLP-1R agonists, were reported (Bomfim et al., 2012; Long-Smith et al., 2013; Bassil et al., 2017). One recent study documented that peripheral exposure to liraglutide resulted in increased insulin sensitivity in the hippocampus of patients with mild cognitive impairment (MCI) (Talbot and Wang, 2014). The administration of GLP-1R agonists was reported to raise the cerebral metabolic rate in various brain regions (Gejl et al., 2012; Daniele et al., 2015). Interestingly, in hyperglycemic conditions, which were shown to enhance ischemic damage and to worsen the clinical outcome after ischemic stroke (Bellolio et al., 2011), continuous infusion of GLP-1 reduced cerebral glucose uptake and increased glucose clearance rates. These effects were largely absent in hypoglycemic conditions (Gejl et al., 2013), indicating that GLP-1 has a regulatory, plasma glucose concentration-dependent effect on brain glucose metabolism, possibly by attenuating the fluctuations in plasma and brain glucose, which is likely to be neuroprotective (Gejl et al., 2014).

3.3. GLP-1R agonists in clinical trials

To date, there are three published clinical trials directly evaluating the effect of GLP-1R agonists on cognitive function in humans. A 6-month, placebo-controlled randomized trial in individuals with AD did not detect an effect of liraglutide on measures of cognitive function (Gejl et al., 2016). A 3-month trail with once-weekly exenatide for obese, antipsychotic-treated patients with schizophrenia spectrum disorder did not observe improvement in the Brief Assessment of Cognition in Schizophrenia (BACS) and the Rey-Osterreith complex figure test (REY) (Ishoy et al., 2017). Our group recently published results of a 4-week, pilot, proof-of-concept, open-label study (Mansur et al., 2017a). We documented significant improvements in the Trail Making Test-B (TMTB) standard score (age and education corrected) (Cohen's $d = 0.64$, $p = 0.009$) and in a composite Z-score comprising multiple cognitive tests (i.e. Digit Symbol Substitution Test [DSST], Rey Auditory Verbal Learning Test [RAVLT], Stroop test) (Cohen's $d = 0.77$, $p < 0.001$). In addition, we also observed improvements in anhedonic symptoms, using the Snaith-Hamilton Pleasure Scale (SHAPS) (Cohen's $d = 0.64$, $p = 0.010$). There were significant methodological differences between these studies, including in the sample composition (i.e. elderly with manifested AD, young and middle-aged adults with psychotic or mood disorders), agents (i.e. liraglutide and exenatide) and neurocognitive tests used, that could explain the discrepancies between results. For example, there is no data on once-weekly exenatide CNS penetration in humans, whereas liraglutide has been shown to cross the BBB (Kastin et al., 2002; Hunter and Holscher, 2012; Secher et al., 2014; Christensen et al., 2015). Nonetheless, one of the most important features of the positive trial from our group was the pre-treatment stratification. Our sample was enriched for executive dysfunction, only subjects with below-average (i.e. 1 SD below norm) performance in the TMTB were enrolled; 101 individuals were screened; of those, 47 (46.5%) met this criteria. Moreover, we also observed moderating effects of pre-treatment BMI and IR on treatment response. The foregoing observation suggests that there are particular subgroups which may be more responsive to GLP-1R agonist's therapy.

Reinforcing the hypothesis that GLP-1R agonists may be useful agents are the results pertaining biological targets. The study of Gejl et al. (2016) (Gejl et al., 2016) reported that liraglutide administration prevented the decline of cerebral glucose metabolism, which has been consistently associated with AD's pathological progression and, consequently, cognitive impairment (Engler et al., 2006; Mosconi, 2005). Our pilot study observed that 4-week treatment with liraglutide resulted in increases in subcortical structures and frontal gray matter (GM) volumes in multiple regions, including the nucleus accumbens and the lateral orbitofrontal (Mansur et al., 2017b). Body weight loss had a moderational effect on these volumetric changes, insofar as increases in frontal and striatal volumes were positively correlated with weight loss in most regions and changes in BMI moderated changes in the right amygdala, nucleus accumbens and rostral middle frontal region. As expected, changes in regional volumes were associated with

improvement in executive function (Mansur et al., 2017b).

GLP-1R agonists have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat diabetes for over a decade and, more recently, for weight loss. Multiple clinical trials have demonstrated that liraglutide is well-tolerated by healthy controls and patients with metabolic conditions. While there were initial concerns about incretin therapy increasing the risk of developing pancreatitis and pancreatic cancer, recent review of pre-clinical and clinical studies has not borne this hypothesis out, and the FDA and EMA have provided reassurance for the clinical and research use of these agents (Egan et al., 2014). Indeed, GLP-1R agonists were well-tolerated in three clinical trials in clinical populations (Gejl et al., 2016; Ishoy et al., 2017; Mansur et al., 2017a). There were no serious adverse events reported and discontinuation rates were relatively low (10–13%). Overall, the evidence indicates that GLP-1R agonists are safe for further testing in mood disorders and/or cognitively impaired populations.

4. Conclusion

Overall, the currently available preclinical and clinical evidence is consistent with GLP-1R agonists as important modulators of the molecular and cellular processes (e.g. neuronal survival) that are thought to underlie cognitive function. Moreover, GLP-1R agonists have been shown to penetrate the CNS in humans and exert measurable and physiologically relevant actions. Among these actions, it is well documented that liraglutide promotes body weight loss, which has been shown to be beneficial for cognitive function. Taken together, these observations suggest that further investigation is warranted in examining the potential beneficial effects of GLP-1R agonists, specifically liraglutide, in measures of cognitive function in a mood disorders population. The safety and availability of GLP-1R agonists also indicate that they are promising candidates for repurposing, and that they may be viable therapeutic options for brain disorders.

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