European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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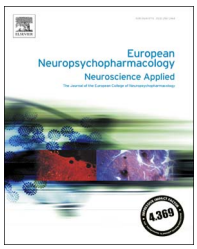

# Treatment with a GLP−1R agonist over four weeks promotes weight loss-moderated changes in frontal-striatal brain structures in individuals with mood disorders

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Received 18 January 2017; received in revised form 9 August 2017; accepted 21 August 2017

**KEYWORDS**
Mood disorders;
Glucagon-like peptide−1;

**Abstract**
Cognitive deficits are a core feature across psychiatric disorders. Emerging evidence indicates that metabolic pathways are highly relevant for the substrates and phenomenology of the cognitive domain. Herein, we aimed to determine the effects of liraglutide, a GLP−1R agonist,

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http://dx.doi.org/10.1016/j.euroneuro.2017.08.433


Please cite this article as: Mansur, R.B., et al., Treatment with a GLP−1R agonist over four weeks promotes weight loss-moderated changes in.... European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.08.433

Liraglutide;
Weight loss;
Neuroimaging;
Gray matter volume

on brain structural/volumetric parameters in adults with a mood disorder. This is the secondary analysis of a 4-week, pilot, proof-of-concept, open-label study. Participants ($N=19$) exhibiting impairments in executive function with either major depressive disorder (MDD) or bipolar disorder (BD) were recruited. Liraglutide 1.8 mg/day was added as an adjunct to existing pharmacotherapy. Structural magnetic resonance imaging (MRI) scanning was obtained at baseline and endpoint. Results showed that at endpoint there was significant weight loss (mean: 3.15%; $p<0.001$). Changes in frontal and striatal volumes were significantly correlated with changes in body mass index (BMI), indicating the weight loss was associated with volume increase in most regions (e.g. $r=-0.561$, $p=0.042$ in the left superior frontal area). After adjusting for intracranial volume, age, gender, and BMI, we observed significant changes from baseline to endpoint in multiple regions (e.g. RR: 1.011, $p=0.049$ in the left rostral middle frontal area). Changes in regional volumes were associated with improvement in executive function (e.g. $r=0.698$, $p=0.003$ for the right superior frontal area). Adjunctive liraglutide results in clinically significant weight loss, with corresponding improvement in cognitive function; changes in cognitive function were partially moderated by changes in brain morphometry, underscoring the interrelationship between weight and brain structure/function.


## 1. Introduction

Cognitive dysfunction is a core dimension/domain of depressive and bipolar disorders (i.e. mood disorders) (Bourne et al., 2013; Lee et al., 2012; Mann-Wrobel et al., 2011; Snyder, 2013). Evidence indicates that cognitive dysfunction in mood disorder encompasses all subdomains and is clinically relevant (Bourne et al., 2013; Lee et al., 2012; Mann-Wrobel et al., 2011; Snyder, 2013). Impairments in executive functions are one of the most replicated findings in clinical and meta-analytical studies. In addition to being a core dimension of psychopathology in mood disorders, cognitive dysfunction (e.g. executive dysfunction) is reported to be an endophenotypic trait and a key cause of reduced psychosocial and workplace functioning (Arts et al., 2008; Bora et al., 2009; McIntyre et al., 2013; Tse et al., 2014).

Results from neuroimaging studies indicate that the central hub subserving executive function is the prefrontal cortex (PFC), with regional specificity noted throughout the PFC subdivisions (i.e. dorsolateral PFC, ventrolateral PFC and anterior cingulate cortex) (Collette et al., 2006; Niendam et al., 2012; Snyder, 2013). Evidence also indicates that multiple integrated neural networks involving functionally and anatomically interconnected nodes in parietal and subcortical regions also contribute to general and cognitive-emotional processes (Collette et al., 2006; Niendam et al., 2012). Moreover, the phenomenology of mood disorders is thought to involve an abnormal activation and/or coordination of distributed networks, including cortical (frontal, temporal and occipital lobes) and subcortical areas (amygdala and hippocampus) (Diener et al., 2012; Phillips and Swartz, 2014; Strakowski et al., 2012). In fact, dysregulation of fronto-limbic circuits was shown to be correlated with degree of executive dysfunction in individuals with bipolar disorder (BD) (Brooks et al., 2010; Li et al., 2012). However, the underlying neural substrates that subserve abnormal brain function in mood disorders remain poorly understood.

More recently, the moderational effect of metabolic comorbidities on cognitive function has been increasingly reported (Bove et al., 2013; Geijselaers et al., 2014; Gluck et al., 2013; Karlamangla et al., 2014; Kenna et al., 2013; Nazaribadie et al., 2014; Samaras et al., 2014; Sanz et al., 2013; Sun et al., 2014; Yogi-Morren et al., 2014). Multiple metabolic abnormalities are independently associated with deficits in executive function. For example, overweight/obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM) have all been consistently shown to negatively impact a variety of cognitive domains (Gunstad et al., 2010, 2007; McCrimmon et al., 2012; Taylor and MacQueen, 2007). Replicated proof-of-concept studies in bariatric surgery have demonstrated that obesity adversely affects cognitive function, wherein individuals receiving bariatric surgery exhibit improvements in cognitive functions post-weight loss and that the weight loss is moderated by improvements in metabolic parameters (Alosco et al., 2014; Siervo et al., 2011). Converging evidence also indicates that overweight/obese individuals with a mood disorder have a greater degree of neurocognitive impairment when compared to normal weight patients (Depp et al., 2014; Watari et al., 2006; Yim et al., 2012). In addition, obesity and/or metabolic dysregulation is associated with structural and functional abnormalities in several brain regions, including, but not limited to, PFC and subcortical structures (Garcia-Garcia et al., 2012; Kullmann et al., 2012). Taken together, it is posited that disturbances in the metabolic milieu and/or overweight/obesity may contribute to brain changes in mood disorders (Bond et al., 2011; Hajek et al., 2013; Hajek et al., 2014; Kuswanto et al., 2013). Notably, alterations in metabolic pathways may be relevant to neurocognitive decline in a subset of individuals with BD or major depressive disorder (MDD)(Bosco et al., 2011; Karunakaran and Park, 2013; Maritim et al., 2003; McIntyre et al., 2008; Reagan, 2012; Tran et al., 2012; Trudeau et al., 2004).

In keeping with the foregoing observations, abnormalities in metabolic pathways represent a prominent and clinically

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