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

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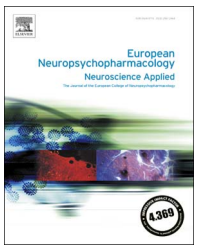

# Increased cortical neuronal responses to NMDA and improved attentional set-shifting performance in rats following prebiotic (B-GOS®) ingestion

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Received 3 July 2017; received in revised form 13 September 2017; accepted 2 November 2017

**KEYWORDS**
Electrophysiology;
Cognition;
Short-chain fatty acid;
Microbiota;
Glutamate

**Abstract**
We have previously shown that prebiotics (dietary fibres that augment the growth of indigenous beneficial gut bacteria) such as Bimuno™ galacto-oligosaccharides (B-GOS®), increased N-methyl-D-aspartate (NMDA) receptor levels in the rat brain. The current investigation examined the functional correlates of these changes in B-GOS®-fed rats by measuring cortical neuronal responses to NMDA using in vivo NMDA micro-iontophoresis electrophysiology, and performance in the attentional set-shifting task. Adult male rats were supplemented with B-GOS® in the drinking water 3 weeks prior to in vivo iontophoresis or behavioural testing. Cortical neuronal responses to NMDA iontophoresis, were greater (+30%) in B-GOS® administered rats compared to non-supplemented controls. The intake of B-GOS® also partially hindered the reduction of NMDA responses by the glycine site antagonist, HA-966. In the

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https://doi.org/10.1016/j.euroneuro.2017.11.001
0924-977X/© 2017 Published by Elsevier B.V.

Please cite this article as: Gronier, B., et al., Increased cortical neuronal responses to NMDA and improved attentional set-shifting performance in.... European Neuropsychopharmacology (2017), https://doi.org/10.1016/j.euroneuro.2017.11.001

attentional set-shifting task, B-GOS® -fed rats shifted from an intra-dimensional to an extra-dimensional set in fewer trials than controls, thereby indicating greater cognitive flexibility. An initial exploration into the mechanisms revealed that rats ingesting B-GOS® had increased levels of plasma acetate, and cortical GluN2B subunits and Acetyl Co-A Carboxylase mRNA. These changes were also observed in rats fed daily for 3 weeks with glyceryl triacetate, though unlike B-GOS®, cortical histone deacetylase (HDAC1, HDAC2) mRNAs were also increased which suggested an additional epigenetic action of direct acetate supplementation. Our data demonstrate that a pro-cognitive effect of B-GOS® intake in rats is associated with an increase in cortical NMDA receptor function, but the role of circulating acetate derived from gut bacterial fermentation of this prebiotic requires further investigation.
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## 1. Introduction

The link between enteric microbiota and brain function is now widely accepted, has been considered as 'a paradigm shift in neuroscience' (Mayer et al., 2014). Mice depleted of microbiota (germ-free mice), display altered behaviours and reduced levels of Brain Derived Neurotrophic Factor (BDNF) and N-methyl-D-aspartate receptors (NMDARs), which are crucial for cognitive function (Sudo et al., 2004). Conversely, gut microbiota enrichment with specific probiotics, live beneficial bacteria, or prebiotics, indigestible compounds that augment the growth of intrinsic beneficial microbes, improve cognitive performance in rodents (Savignac et al., 2015; Vázquez et al., 2015; O'Hagan et al., 2017) and humans (Schmidt et al., 2015; Steenbergen et al., 2015). The reduction of attentional bias to negative emotional stimuli in healthy volunteers following a dietary supplementation with the Bimuno™ galacto-oligosaccharide (B-GOS®) prebiotic (Schmidt et al., 2015), may be a corollary of increased levels of NMDAR subunits which we have observed in the rat frontal cortex following B-GOS feeding (Savignac et al., 2013). However, the functional correlates of these changes have not been explored.

The prebiotic properties of B-GOS® have been extensively studied, and the product which contains a mixture of galacto-oligosaccharides of several lengths (2–7 saccharides) has been consistently shown to selectively increase *Bifidobacteria* and, to some extent, *Lactobacilli* in both humans and animals (Tzortzis et al., 2005; Depeint et al., 2008; Vulevic et al., 2008; Silk et al., 2009; Savignac et al., 2013). Understanding how B-GOS® modulates NMDARs has important implications for both the prevention of the age-related decline in cognitive function (Nicolle and Baxter 2003), and the treatment of neuropsychiatric disorders such as schizophrenia, where aberrant glutamate neurotransmission and cognitive deficits cannot be rescued by conventional medication. Given that the loss of NMDAR function impairs cellular responses in the rodent cortex (Rompala et al., 2013), we hypothesise that the elevated cortical GluN1 and D-serine following B-GOS® ingestion (Savignac et al., 2013), increases cortical NMDAR-mediated neural activity, and related behaviours. In the latter instance, based on existing data, increased cortical NMDAR function in healthy animals may improve attentional set-shifting performance (cognitive flexibility), a prefrontal cortex (PFC)-dependent behaviour often impaired by NMDAR antagonists (Neill et al., 2010; Wallace et al., 2014), or the natural decrease in cortical NMDAR levels during aging (Nicolle and Baxter 2003; Rodefer and Nguyen, 2008). However, there are no studies demonstrating improved cognitive flexibility in experimentally naïve rodents following an elevation of NMDARs, and/or their function, in the PFC. The increase of central NMDAR subunits in the rat brain following B-GOS ingestion, provides a model to test this.

There is also an urgent need to ascertain the mechanisms that underlie the central effects of B-GOS®, so that key intermediaries of microbe-brain interactions can be revealed. The short-chain fatty acids (SCFAs) that arise from bacterial fermentation of dietary carbohydrates in the host gut, have been suggested to be one such mediator (Sarkar et al., 2016). Fermentation of B-GOS has been shown to produce significant amounts of acetate, and moderate amounts of butyrate (Grimaldi et al., 2016, 2017). Both of these SCFAs can have central effects, particularly at the epigenetic level where they both influence the expression of brain histone deacetylases (HDACs) (Soliman et al., 2012; Han et al., 2014), but a link between metabolic acetate and NMDARs has also been demonstrated (Hirose et al., 2009; Singh et al., 2016). In this regard, if acetate is involved in B-GOS® mediated changes of NMDAR function, then direct acetate supplementation might be expected to have similar effects on central NMDAR levels as the prebiotic itself.

The aim of the current study was to, first, confirm with in vivo iontophoresis electrophysiology increased NMDAR function in the rat frontal cortex following B-GOS® intake alone, or in the presence of the NMDAR glycine-site antagonist, HA-966. Second, test if administration of B-GOS® facilitated cognitive flexibility, based on the prebiotic-mediated elevation of cortical NMDARs. Third, explore the role of acetate in the actions of B-GOS® by (i) measuring plasma and brain levels of this SCFA in B-GOS® -fed and control rats, and (ii) quantifying in all animals the expression of frontal cortex Acetyl Co-enzyme A Carboxylase (ACC) mRNA. Earlier work has demonstrated that a single systemic injection of acetate into rats increases the activity of hypothalamic ACC (Frost et al., 2014). This enzyme metabolises the Acetyl Co-enzyme A that is produced from the acetate sequestered in tissues. The abundance of cortical ACC mRNA therefore, was used as an indicator of acetate metabolism. In addition, the expression of HDAC(1–4) genes in the cortex were measured to evaluate whether B-GOS®, via acetate, affects epigenetic processes.

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