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To cite this article: Philippe de Timary, Sophie Leclercq, Peter Stärkel & Nathalie Delzenne (2015) A dysbiotic subpopulation of alcohol-dependent subjects, Gut Microbes, 6:6, 388-391, DOI: [10.1080/19490976.2015.1107696](https://doi.org/10.1080/19490976.2015.1107696)

To link to this article: <http://dx.doi.org/10.1080/19490976.2015.1107696>



Published online: 04 Jan 2015.



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## A dysbiotic subpopulation of alcohol-dependent subjects

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The vast majority of studies that assessed the importance of biological factors for the development of psychiatric disorders focused on processes occurring at the brain level. Alcohol-dependence is a very frequent psychiatric disorder where psycho-pharmacological interventions are only of moderate efficacy. Our laboratory has recently described that a subpopulation of alcohol-dependent subjects, that accounted for approximately 40% of individuals tested, presented with an increased intestinal permeability, with a dysbiosis, with alterations in the metabolomic content of faeces - that could play a role in the increased permeability - and finally with a more severe profile of alcohol-dependence than the other non-dysbiotic subpopulation. In this addendum, we discuss the implications of our observations for the pathophysiology of alcohol dependence where we try to discriminate which addiction dimensions are likely related to the gut microbiota alterations and whether these alterations are the cause or the consequence of drinking habits.

**Keywords:** alcohol dependence, alcohol use disorders, behavior, depression, gut permeability, gut-brain axis, gut microbiota, leaky gut, negative reinforcement

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Submitted: 03/19/2015

Revised: 10/07/2015

Accepted: 10/08/2015

<http://dx.doi.org/10.1080/19490976.2015.1107696>

**Addendum to:** Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, Windey K, Tremaroli V, Backhed F, Verbeke K, de Timary P and Delzenne N. Intestinal permeability, gut bacterial dysbiosis, and behavioral markers of alcohol dependence. *Proceedings of the National Academy of Science* 2014; 111: E4485–93.

### Introduction

Numerous factors are involved in the development of psychiatric disorders. According to a generally accepted biopsychosocial model of disease,<sup>1,2</sup> most psychiatric disorders are expected to result from the complex interaction between a panel of biological events, psychological factors (related for example to the personality or affects) and the quality of social interactions. Among psychiatric disorders,

alcohol-dependence is one of the most frequent ones and currently represent the second cause of death and morbidity worldwide. Alcohol dependence causes an extremely high burden on society, due to its consequences on health, on criminality and hazards to others.<sup>3–5</sup> However, a majority of alcoholic subjects do not even have access to therapy.<sup>6</sup> Hence, treating alcohol-dependent (AD) subjects is certainly an important challenge for the medical community, and a multidisciplinary approach could be promoted in order to integrate contributions from various fields of expertise, including psychological, social and biological approaches. Psycho-pharmacological interventions dedicated to the treatment of alcohol-dependence targeting receptors for neurotransmitters have up to now permitted to obtain some improvements in the management of the disorder, but the effects are at best of moderate magnitude.<sup>7,8</sup>

Recent interest on the possible role of the gut and of the gut microbiota in the development of psychiatric disorders, mainly arises from animal studies that clearly established that processes occurring at the level of the intestine may profoundly affect behaviors.<sup>9</sup> Studies of the impact of gut dysbiosis on psychiatric disorders have mainly focused on 2 domains of psychiatry : the development of mood symptoms, for instance, depression and anxiety (See review in.<sup>10,11</sup>) and the development of profound social impairment as observed in autistic spectrum disorders.<sup>12–14</sup> The paper we are commenting on here,<sup>15</sup> even though focusing on alcohol-dependence, also relates to depression and anxiety, as these

symptoms are an important dimension of alcohol-dependence. In the first part of the discussion, these aspects will be evoked at the light of the negative reinforcement process, that is a major dimension of the addictive process,<sup>16</sup> especially in chronic addiction. However, alcohol-dependence is a particular psychiatric disorder: being an addiction, it also involves important alterations of the metabolism and eating habits because the consumption of ethanol usually accounts for a very large portion of the total caloric intake in this population.<sup>17-19</sup> Not surprisingly, these abnormal eating patterns likely influence the composition of the gut microbiota. Furthermore ethanol *per se* may also interfere with the gut microbiota and the gut barrier, and the article we discuss here at least partially provides answers to the question of the role of ethanol in the dysbiosis observed in AD subjects.

### A Role for Dysbiosis in the Negative Reinforcement Process

Frequently in young adults exposed to alcohol-drinking,<sup>20</sup> or in some subpopulations of alcohol-dependent subjects,<sup>21</sup> presenting impulsive personality profiles, alcohol consumption is essentially motivated by obtaining a positive reinforcement, i.e. a feeling of euphoria and achievement, and due to positive expectancies.<sup>22</sup> However, frequently, in other larger subpopulations of alcohol-dependent patients, and most often in later stages of the addiction, once it has completely developed, drinking becomes a compulsive process.<sup>23</sup> It means that drinking is essentially a way to escape negative affects and feelings. This also means that in situations of distress, alcohol-dependent subjects start drinking in order to escape this negative feeling and that distress impairs the ability of subjects to self-regulate their drinking. The article by Leclercq et al, shows that subjects with increased intestinal permeability associated with an important dysbiosis, with alterations in the metabolomic profiles and with persistent systemic inflammation, also presented with increased symptoms of depression, anxiety and craving at the end of alcohol withdrawal. Depression and anxiety that

have been shown in previous studies to be correlated with craving,<sup>24,25</sup> are the behavioral expression of negative reinforcement processes of addictions with a negative affect being the drive for alcohol consumption. A large number of studies in animal models have proposed that ethanol interacts with the brain to develop a negative affect. They explain negative reinforcement processes by dysregulation of numerous neurotransmitter systems and activation of the brain stress system through activation of CRH liberation and a decrease in NPY brain anti-stress activity.<sup>16,26</sup>

Our observation suggests that besides important direct effects of ethanol on the brain, a part of the processes might also arise from the gut. Other authors have previously proposed a role for the gut in the development of addiction,<sup>17,27</sup> but essentially through endocrine processes. The data from the article we comment on here suggest that it may also involve a dysbiosis. Several pathways may be involved for the gut microbiota to affect drinking habits. The gut microbiota secretes more than 100 different metabolites,<sup>28</sup> including neurotransmitters such as dopamine, serotonin, noradrenaline or GABA. The pathways related to these neurotransmitters are all affected by the development of alcohol-dependence. The microbiota and the increase in permeability may also interact through the enteric tract with the vagus nerve.<sup>29</sup> It may affect the stress system.<sup>30</sup> Finally, it generates a mild form of chronic inflammation, related to the increased gut permeability,<sup>31,32</sup> that is currently considered an important factor for the development of depression.<sup>33</sup> Overall because ethanol may affect the gut and hence the various pathways described above, the gut may be considered as another important target for ethanol, and mediate through the gut-brain axis some of the behaviors observed in AD subjects, besides the direct effects of ethanol at the level of the brain.

It is even not totally unlikely that a part of the negative reinforcement processes that have been observed at the level of the brain and that are deemed an essential dimension of addiction.<sup>26</sup> could also partially result from an interplay between gut and brain processes. For instance, the

dysregulation of the brain stress system or some of the neurotransmitter alterations could possibly partially be due to an effect of ethanol on the gut microbiota.

### Is Dysbiosis Playing a Role in the Entire Population of Alcohol-Dependent Subjects ?

The data of the article by Leclercq and colleagues showed that only a subpopulation of about 40% of AD subjects presented with important modifications of the gut microbiota and an increased intestinal permeability. There is something very specific to that population that, as described above, presented with markers of severity of alcohol-dependence, through negative reinforcement processes. The remaining population of AD-subjects, who do not have a dysbiosis, seemed to be different at the behavioral level as they showed less severe levels of depression, anxiety and craving, already at the beginning of alcohol withdrawal. The difference was even much stronger at the end of the detoxification, as this non dysbiotic group almost totally recovered from symptoms of depression, anxiety and craving when compared with a control group, suggesting that the negative reinforcement processes had completely disappeared after 18 d of abstinence. Two consequences may be drawn from this observation. Firstly, in the dysbiotic group, the persistence of signs of depression, anxiety and craving after 18 d of abstinence, means that the reinforcement processes in this population is not dependent anymore on the drinking, but possibly on processes occurring at the level of the gut and related to the dysbiosis that still persists. As previously demonstrated, the persistence of negative reinforcement may be very important for relapse prognosis,<sup>34-36</sup> but this dimension still deserves to be tested to ascertain the importance for the outcome of disease. This may also make that the dysbiotic subpopulation of AD subjects prone to specific interventions at the level of the gut microbiota. Secondly, in the non-dysbiotic group that exhibited criteria of reduced severity, the negative reinforcement process was also present at the beginning of alcohol withdrawal when the

subjects were still under the effect of ethanol, since signs of depression, anxiety and craving were observed. The negative reinforcement processes in this situation likely result from a direct effect of ethanol occurring at the level of the brain through the classical « dark side of addiction », as hypothesized previously.<sup>16</sup> However, a role for the gut microbiota cannot be formally excluded in this population. It is conceivable that ethanol also interacts with a normal gut microbiota to induce depression, anxiety and craving, somehow participating in the allostatic load induced at the brain level by the addiction. Overall, what our data suggest is that this non dysbiotic group is characterized by a markedly attenuated form of negative reinforcement processes, both in amplitude and duration.

### Which Pathways of the Gut-Brain Axis are Involved the Development of Alcohol-Dependence?

Another important aspect is the issue of the mechanisms involved in the gut-brain communication to explain the development of these negative reinforcement processes. There is currently only limited data available to answer this question. The numerous potent pathways that have been invoked above to explain a communication between the gut and the brain may all have an importance for the development of the symptomatology of alcohol-dependence: the direct production of metabolites by the gut microbiota and that may be released in the circulation, the abnormal functioning of the hypothalamo-hypophyso-adrenal pathway that may be linked to depression or anxiety or a dysregulation of the vagal nerve activity that may have an impact on affect regulation.<sup>37</sup> may all be of importance. However, to date, the strongest evidence exists for the inflammatory pathway as a mediator in the gut-brain interplay. Preclinical as well as clinical studies have shown the potent role of inflammation for the development of alcohol-dependence, as nicely described in a recent review article.<sup>38</sup> Furthermore, in the study commented here, as well as in previous studies from our group.<sup>32</sup>

proinflammatory markers were related to the gut permeability, and in the same population these markers were shown to correlate positively with craving at the beginning of withdrawal while the anti-inflammatory cytokine IL-10 correlated negatively with depression, anxiety and craving at the end of withdrawal.

It is note-worthy that negative reinforcement processes are not the only mechanisms involved in the development of addiction. Hence, the possibility of a role for the gut microbiota and dysbiosis in the development of positive reinforcement, or in the cognitive deficits involved in the development of addiction should also be evaluated in future studies.

### Is Alcohol Drinking the Cause of Alterations in the Gut Microbiota and in the Gut Barrier Function?

Our test retest design at the beginning and end of alcohol withdrawal as well as our careful evaluation of the alcohol intake by patients permitted to evaluate the effect of ethanol on the gut.

Ethanol consumption clearly played an important role in the increase in gut permeability in the dysbiotic group, as permeability totally recovered after the period of abstinence. But ethanol was not sufficient *per se*, and we propose that the dysbiosis could be part of the alteration of the gut barrier upon alcohol consumption, as no increase in permeability was observed in the non-dysbiotic group, despite the consumption of alcohol.

The role of ethanol intake on the composition of the gut microbiota was not obvious from the data we obtained. On the one hand, we did not observe differences in alcohol intake between the dysbiotic and non-dysbiotic group, suggesting that the difference in composition of the gut microbiota might not be the consequence of drinking. Furthermore, the total concentration in bacteria and in most bacterial families, genera or species failed to recover at the end of alcohol withdrawal. These observations therefore suggest that the composition of the gut microbiota is likely independent of the drinking habit. For instance, *Faecalibacterium prausnitzii*, a bacteria belonging to the *Ruminococcaceae*

family exhibiting important anti-inflammatory properties,<sup>39</sup> which was largely depleted in the dysbiotic subgroup compared with the control and non-dysbiotic groups, remained completely unaffected by drinking cessation. The resistance of the gut microbiota of the dysbiotic group to abstinence was further supported by the observation of only scarce modifications of the metabolomic composition of the stool that remained completely different from that of the control or non-dysbiotic groups at the end of detoxification.

On the other hand, some specific genera, such as the *Lactobacillus* or *Bifidobacteria*, that may also be important for inflammation, presented important variations during the period of withdrawal, suggesting at least some sensitivity to the effects of ethanol. In addition, a period of 2 to 3 weeks of abstinence may not be sufficient to allow a complete recovery of the microbial composition, as it is also not sufficient to allow a total recovery of the inflammation.<sup>31,32</sup> and of some cognitive functions.<sup>24,40</sup> Hence, to ascertain that the gut microbiota of dysbiotic AD subjects is not totally dependent on the effect of ethanol, it would deserve being retested after several months of abstinence.

The apparent relative independence of the gut microbiota from the exposition to ethanol raises an interesting issue: could the alteration in the gut microbiota be a precursor to the development of alcohol-dependence in some subjects? The existence of a primary dysbiosis has for instance been shown in Intestinal Bowel Syndrome (IBS) and could also exist in alcohol-dependence. It should first be stressed that the AD patients of the study did not present with an IBS, as none of them presented with diarrhea at the end of alcohol withdrawal. Longitudinal studies should however be conducted to answer the question of a persistent dysbiosis in this population to determine whether this dimension would participate to the development of alcohol-dependence. In other words, the issue is whether some specific combinations of microbes within the intestine may predispose to the development of this dramatic disorder, a bit like genetic factors that have

been shown to be crucial for the condition.<sup>41</sup>

Even if this work raises a lot of questions about the mechanism by which gut microbiota alteration may act on gut barrier and brain function, it is the first paper proposing a new target - namely the gut microbiota- in the management of the crucial and extended worldwide problem of health represented by excess of alcohol consumption and dependence.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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