been hypothesised, there is not convincing evidence to date explaining if and how modifications of the gut-microbiome might translate in mental health phenotypes. This resulted in a number of clinical trials reporting negative findings, likely due to the lack of specificity of the proposed interventions [3]. Identifying specific gut-microbiome to-brain paths is therefore a research priority, before we engage in further trials.

Based on a consistent number of evidence showing an independent contribution of the gut-microbiome and the endocannabinoid system for anhedonia [3-5], we tested the hypothesis that the endocannabinoid system mediates the association between gut-microbiome diversity and anhedonia using data from a general population cohort.

Methods: We used longitudinal data collected from 786 volunteer twins recruited as part the TwinsUK register. Our hypothesis was tested with a multilevel mediation model using family structure as random intercept. The model was set using alpha diversity (within-individual gut-microbial diversity) as predictor, serum and faecal levels of the endocannabinoid palmitoylethanolamide (PEA) as mediator, and anhedonia as outcome. Anhedonia was measured with a well-validated set of items from the Hospital Anxiety and Depression Scale.

Analyses were adjusted for obesity, diet, antidepressant use, sociodemographic and technical covariates. Data were imputed using multiple imputation by chained equations.

Results: The mean age of the sample was 65.2±7.6. A proportion of 93% of the sample were females, 27% were obese, and only 5% ever received an antidepressant. We found a direct, significant, association between alpha diversity and anhedonia (β=-0.37; 95%CI: -0.71 to -0.03; P=0.03). Faecal levels of the endocannabinoid palmitoylethanolamide (PEA) mediated this association: the indirect effect was significant (β=-0.13; 95%CI: -0.24 to -0.01; P=0.03), as was the total effect (β=-0.38; 95%CI: -0.72 to -0.04; P=0.03), whereas the direct effect of alpha diversity on anhedonia was attenuated fully.

Conclusion: Here we provide the first evidence showing that the association between gut-microbial diversity and anhedonia is mediated by the endocannabinoid system.

In particular, we found that to reduced microbial diversity corresponded increased faecal excretion of the endocannabinoid palmitoylethanolamide (PEA), which in turn led to more severe anhedonia/amotivation. Reduced microbial diversity is considered a sign of a "unhealthy" microbiome and it has been associated with a number of detrimental health outcomes, including psychosis and depression, which often manifest with anhedonia [3,5]. PEA is considered the endogenous equivalent of cannabidiol (CBD), as it shares a similar pharmacodynamic [4]. Similar to CBD, PEA has neuro-protective and anti inflammatory properties [4]. These considerations explain the direction of findings.

Our results shed light on the biological underpinnings of anhedonia and suggest the gut microbiome-endocannabinoid axis as a promising therapeutic target in an area of unmet clinical need.

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Structural correlates of modular organization of signal transmission in the primate somatosensory cortex

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Introduction: Axonal connections of column size cortical regions exhibit patchy distribution all over the primate cerebral cortex. The axonal patches represent specific target sites as e.g. columns of similar orientation preference in the visual cortex. However, axonal connections also densely distribute outside of the patches without any apparent grouping. Instead, the out-patch axons exhibit a radial spreading from the origin towards probably distant target sites including the patches. Interestingly both patch and out-patch axons form axon terminal-like structures suggesting their role in synaptic transmission.

Aim: The aim of our study is to know whether axons play a similar role in the propagation of activity and dissemination of information within and outside of the patches. To answer this question morphological properties of reconstructed axons within and outside of the patches were compared for intra- and inter-areal connections in the somatosensory cortex of squirrel monkeys.

Methods: Distal finger pad representations [1] of six squirrel monkeys that were injected with BDA via iontophoresis in area 3b (3 cases) and area 1 (3 cases). Aldehyde fixation was

made by transcardial perfusion after 10-20 days survival. Series of 50 μm thick horizontal, vibratome sections were collected at regular intervals from the flattened cortex. Standard ABC protocol was used to visualize BDA labelling with nickel intensified DAB as the chromogen. Sections were then osmicated and flat embedded in Durcupan. Intra and Inter areal axons [2] of areas 3b and 1 were studied. Axonal patches were mapped and outlined by using Neurolucida. Reconstruction of the BDA labelled axonal fibres was also made with Neurolucida at high magnification within and outside of the axonal patches. Tortuosity, Inter-varicosity distance, Thickness, Bouton convergence, and Density of varicosity thickness of the individual axonal segments within and out of the patches were compared. The abundance of axons bearing boutons with stalks were also studied within and outside of the patches.

Summary: Based on data analysis our findings suggest that axons have similar tortuosity but different bouton density within and outside of the patches. Specifically, intrinsic connections exhibit higher bouton density within than outside of the patches. Moreover, we measure the Inter-varicosity distance a physical distance of an axon between two boutons which is significantly higher in out patch axons than the patch. Furthermore, the bouton convergence which is the distance from main axon bouton to neighbouring axon boutons is much higher within the patch than out patch. Finally, we measure the thickness of axonal processes within and out of the patches and we found that the out patch long-range axons are much thicker than in patch axons which may lead to faster signal transmission along the out-patch axons.

Conclusion: The increased bouton density accompanied by extensive axonal convergence (Cris-cross) could result in a highly efficient way of signal transmission in terminal arborization patches of the cerebral cortex. In contrast, the long-range thick axons outside the patches could provide input to extra classical receptive field and form the structural correlate of cortical plasticity.

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Alcohol use impacts reward network structure in bipolar disorder

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Widespread alterations involving frontal, temporal and parietal cortical regions, particularly in those related to reward and emotion regulation have been described following non-dependent alcohol use and independently in bipolar disorder (BD) [1–3]. Individuals with BD who engage in non-dependent levels of alcohol use have demonstrated a poor clinical trajectory, with increased numbers of depressive, and (hypo)manic episodes [4,5]. Therefore, people with BD, who are exposing themselves to non-dependent alcohol use are at increased risk of experiencing a depressive or (hypo)manic episode and thus relapse in the disorder. Understanding the neuroanatomical impacts associated with non-dependent alcohol use within the reward network, may aid in explaining the conferred vulnerability to relapse associated with non-dependent levels of alcohol use in BD.

Bipolar Disorder (DSM-V-TR) and psychiatrically healthy participants underwent T1-weighted (MPRAGE) MRI scanning, and the AUDIT-C questionnaire to assess alcohol use. Reward related processes are underpinned by the interaction of network parts, however, only a limited number of the regions involved consistently display thickness or volumetric reductions in association with non-dependent alcohol use or BD. The regions which are persistently found to be impacted were defined bilaterally as the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and insula and were parcellated based on the Desikan-Killiany atlas using FreeSurfer (v.5.3.0)7;8. Cortical thickness was examined for an effect of alcohol use and compared between BD and control groups covarying for age, sex and diagnosis.

For all participants alcohol was associated with thinning of the left ACC (T=-2.984, pFDR=0.016), OFC (T=-2.508, pFDR=0.025), and insula (T=-2.385, pFDR=0.025). Despite the groups consuming similar amounts of alcohol (HC: n=46, mean years of age $\pm$SD= 41$\pm$14; BD: n=40, 43$\pm$13) (U=-713.5, p=0.072), for BD participants increasing, yet non-dependent, alcohol use was associated with cortical thinning in the left ACC (T=-3.187, p=0.003), and left dlPFC (T=-2.237, p=0.032), which was not present in controls (ACC: T=-20.914, p=0.366; dlPFC: T=0.339, p=0.737), and no difference in cortical thickness between the groups.

Human behaviour is in part describable as the interaction of connected elements of a complex system, the brain. Together anterior cingulate, dorsolateral and orbitofrontal cortices function within networks to generate a subjective urge to consume alcohol. The efficient functioning of these prefrontal areas is suggested to maintain non-dependent alcohol use, due to less craving induced activation coupled with stronger cognitive control. However, cognitive inflexibility arising due to structural alterations, may contribute to the continuing use of alcohol despite negative impacts.