Fungal Fumes in Faeces - Hidden Culprit Behind Parkinson’s Disease? A Faecal Metabolomics Study

Introduction
Accumulating evidence implicates the brain gut axis in the pathogenesis of Parkinson’s disease (PD). Altered gut permeability may result in afferent vagal transport of an unknown antigen or toxin to the central nervous system, leading to the characteristic dopaminergic neurodegeneration. A study in fruit flies identified the possible role for fungal metabolites, for example 1-octen-3-ol, in a loss of dopamine activity. We investigated the hypothesis that such fungal metabolites might arise from the faeces. We present the results of an evaluation of the faecal metabolome by assessing volatile organic compounds (VOCs) in PD patients.

Methods
Using solid phase micro-extraction and gas chromatography and mass spectrometry VOCs were extracted from faecal samples from 35 PD patients (69% male; age 67±8 years; disease duration 11±5 years) and 35 healthy controls (37% male; age 65±8 years). VOCs were identified using automated mass-spectral deconvolution and identification system software and the national institute of standards and technology library. Distinguishing compounds were identified using fold change and t-test and corrected for multiple comparisons; group associations were determined using principal components analysis (PCA) and dendrograms. Findings were compared among groups and correlated with main variables.

Results
A mean of 63 VOCs were found from PD samples and 74 from controls (p<0.007). The abundance of VOCs in PD and all controls was compared: 33 differed, 7 of which persisted after correction for multiple comparison, including 2-octanone. PCA showed distinct clustering of groups by disease status (Figure 1). In PD, there was an increased abundance of 2-methyl-6-methylideneoct-2-ene, (6Z)-2,6-dimethyl-2,6-diene and 7-methyl-3-methylideneocta-1,6-diene and a decreased abundance of cyclohexanecarboxylic acid and methyl pentanoate. Several of the VOCs which increased in PD were fungal metabolites. There was no differences in VOCs in patients compared by disease stage.

Conclusions
Metabolomic characterisation in PD patients demonstrates a distinct profile to healthy controls and an increased abundance of fungal metabolites, suggesting a potential role of fungal dysbiosis in PD pathogenesis.

Consequences of Using the Rome IV Criteria to Diagnose Irritable Bowel Syndrome

Introduction
There are few studies examining implications of applying the Rome IV criteria for irritable bowel syndrome (IBS), in preference to the previous gold standard, the Rome III criteria. We conducted a cross-sectional survey of over 1000 individuals who self-identified as having IBS in order to examine this issue.

Methods
We collected complete demographic, symptom, mood, and psychological health data from 1375 adult subjects in the UK community with IBS. We applied both the Rome III and the Rome IV criteria simultaneously to examine what proportion met each of these diagnostic criteria for IBS. We measured the level of agreement between the Rome III and Rome IV criteria, and assessed for presence of an alternative functional bowel disorder in individuals who no longer met diagnostic criteria for IBS with the more restrictive Rome IV criteria. Finally, we compared characteristics of individuals who met only Rome III criteria with those who met Rome IV criteria.

Results
In total, 1080 (78.9%) of 1368 individuals with IBS met the Rome III criteria. In contrast, only 811 (59.1%) of 1373 individuals with IBS met the Rome IV criteria. Agreement between the criteria was only moderate (Kappa = 0.50). The reasons for not meeting the Rome IV criteria for IBS among those meeting the Rome III criteria are shown in Table 1. Of those people no longer meeting Rome IV criteria for IBS, 33 (11.5%) met Rome IV criteria for functional constipation, 118 (41.3%) functional diarrhoea, 68 (23.8%) functional abdominal bloating or distension, and 67 (23.4%) an unspecified functional bowel disorder. This meant that, of those individuals with Rome III IBS who did not meet the Rome IV criteria for IBS, only 11.5% were reclassified into another functional bowel disorder where licensed and evidence-based
therapies are available. Individuals with Rome IV-defined IBS had more severe symptoms, and higher levels of mood disorder and poor psychological health, compared with those who only met the Rome III criteria for IBS (P < 0.001).

Conclusions Moving from the Rome III criteria to Rome IV IBS has substantial implications, both for individuals who believe they suffer from IBS, and for the spectrum of disease severity seen. Understanding the impact of these changes on clinical trials of novel therapies will be important.

Abstract OWE-13 Table 1. Reasons for not Meeting the Rome IV Criteria for IBS Among those Meeting the Rome III Criteria.

<table>
<thead>
<tr>
<th>Reason for Not Meeting Rome IV Criteria</th>
<th>Met Rome III Criteria, but not Rome IV Criteria (n = 286)</th>
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<tbody>
<tr>
<td>Reported abdominal discomfort, rather than abdominal pain (%)</td>
<td>26 (9.1)</td>
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<tr>
<td>Did not report abdominal pain at the required frequency (%)</td>
<td>253 (88.5)</td>
</tr>
<tr>
<td>Other reasons (%)</td>
<td>7 (2.4)</td>
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Abstract OWE-14 SYMPTOM BURDEN IN CHRONIC CONSTIPATION IS PREDICTED BY SENSORY DOMAINS, NOT STOOL FREQUENCY

Introduction Clinical practice and trial endpoints studying chronic constipation typically define therapeutic success by increasing stool frequency, using this as a marker for improvement in symptom burden and patient quality of life (QOL). However, given constipation engenders numerous other distressing symptoms, such as abdominal pain, bloating, tenesmus or nausea and vomiting, we investigated the predictors of symptom burden and QOL.

Methods 768 patients attending with chronic constipation to a tertiary service underwent quantification of symptom measures in a prospective cohort study design. The validated PAC-sym and –qol questionnaires were used as markers for overall symptom burden and QOL. Transit studies were performed in all patients using radio-opaque marker technique. Effect sizes of demographics, stool frequency and GI symptoms in accounting for total symptom burden and QOL were calculated. Analyses were multiple comparison corrected by false discovery rate.

Results Predictors of symptom burden frequency and severity of pain (including relation to defecation attempts) were the strongest predictors (all corr-p<0.0001, Cohen’s D ~0.8, large effect size) (Fig 1). Frequency of stool passage was a weak predictor (corr-p<0.0001, Cohen’s D ~0.48, small-medium effect size).

Predictors of quality of life: abdominal bloating and pain severity were the strongest predictors of QOL (all corr-p<0.0001, Cohen’s D >0.7, medium-large effect size). Stool frequency and transit measures were non-significantly related to total QOL.

Conclusions Sensory symptoms (pain and bloating), not features of disturbed motility (stool frequency and transit), are the most predictive in determining overall symptom burden and QOL. Endpoints of clinical trials should focus on attenuating these symptom measures rather than merely changing bowel habit.

Values of effect sizes are in Cohen’s d, wherein roughly a value of 0.2 equates to a small effect size (S d), 0.5 a medium effect size (M d) and 0.8 a large effect size (L d). Abbreviations: ODS, obstructed defecation score.

Abstract OWE-14 Figure 1: Determinants of symptom burden and QOL in chronic constipation.