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Novel outcomes for Fecal Microbiota Transplantation in Healthy Volunteers: A Case Report

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ABSTRACT

Faecal Microbiota Transfer/Transplantation (FMT) has seen impressive clinical outcomes in treating a range of disorders and illnesses. However there are few studies addressing short-term or long-term outcomes for healthy volunteers undergoing FMT with no predetermined specific therapeutic goals. This case examines the personal experience of two healthy subjects who underwent FMT and reported novel outcomes post transfer. Outcomes included change in body odour, mood and cognition. Further studies are required to illuminate the extent of extra-gastrointestinal effects associated with FMT and the mechanisms by which they occur.

Keywords: Faecal microbiota transplantation; Outcomes; Healthy volunteers; Cognition; Mood; Body odour

INTRODUCTION

Faecal Microbiota Transfer (FMT) refers to the transplantation of stool from an allogeneic donor to the recipient's gastrointestinal tract[1]. While the mechanism by which FMT provides its therapeutic benefit has not been completely elucidated, previous studies have shown that FMT results in distinct changes in gut microbiota[2,3].

FMT has seen impressive clinical outcomes including high response rate (>90%) in restoring gut microflora in patients suffering from a number of diseases, most notably recurrent *Clostridium difficile* infection[4,1]. These successes have led to further studies assessing FMT and its effectiveness in treating other diseases, including ulcerative colitis and Crohn's disease[5,6,7]. Current FMT studies have reported some short-term and long-term effects in patients with various pathologies. However there are very few studies that assess the response to FMT in the context of regular gut function in healthy participants. Published studies assessing outcomes of FMT in healthy human subjects address clinical observations and changes in gut microbiome including a shift towards donor gut flora composition. Additionally these studies have reported findings on adverse reactions and tolerance in participants[4,8]. To date there are no studies that address any extra-gastrointestinal effects of FMT in healthy human volunteers.

Recent literature has shown that changes in gut microbiota have an effect on brain health including behavioural and cognitive outcomes[9,10,11]. This bidirectional relationship between gut and brain health has been termed the gut-brain axis with recent extensions of this concept now being termed the microbiota-gut-brain axis[12,13]. The gut-brain axis concept has led researchers to consider the intentional modulation of gut microbiota (through diet and other methods) as treatments for a range of behavioural and cognitive disorders. Multiple studies have documented FMT as a potential treatment for Parkinson's disease, Alzheimer's disease & autism[14,15].

There are currently no published studies that address extra-gastrointestinal outcomes for healthy subjects undergoing FMT, despite knowledge that the bidirectional relationship of the gut-brain axis suggests a range of extra-gastrointestinal effects could result from FMT procedures. Recent studies have proposed FMT as a therapy for a number of extra-gastrointestinal diseases. These studies have documented the effects of gut microbiota modulation on cognition and mood. Though the clinical evidence for the effects of FMT on mood and cognition are in their infancy, there is some suggestion that FMT could have a range of therapeutic applications that are yet to be explored. This case report details the experience of two healthy volunteers who received FMT and recorded outcomes related to body odour, mood and cognition.

CASE REPORT

This report focuses on the self-reported experiences of two healthy volunteers, one male and one female who were aged 67 and 60 respectively at the time of the FMT procedure. Both participants were considered healthy volunteers for the duration of treatment and the reporting period with no major health complications. The female volunteer reported psoriasis as the only pre-existing autoimmune disorder.

Both subjects reported any physical symptoms experienced in a four week period leading up to FMT. The male subject reported no physical symptoms and the female subject reported low energy and trouble sleeping. Additionally both candidates also completed a depression, anxiety and stress scale (DASS21) report prior to FMT dose outlining any pre-existing mental health conditions experienced in 4 weeks leading up to the procedure[16] . Neither subject displayed significant signs of depression, anxiety or stress prior to FMT.

Both participants work in the medical field with male participant a practicing medical doctor and the female participant a research scientist in mucosal immunology. The participants are a couple in cohabitation.

25-30g sample of donor stool was prepared by suspending a sample in 20ml of physiologically buffered normal saline, strained and decanted into a sterile enema bottle. Donor sample solution was delivered by rectal enema as per clinically developed protocol and the participant laid down on left side with pillow under hip for 10 minutes and was told to avoid bowel movement for as long as possible. Participants gave informed consent for this study.

The reporting period for the two participants commenced immediately after FMT had been administered. The female participant underwent a single dose of FMT and the male subject received two doses.

Table 1- Participant Experience 7 Days Post Fmt After First Dose

Participant Experience Within 7 Days of FMT, Initial FMT Procedure		
	Female Participant	**Male Participant**
Sleep (Average Hours Per Night)	7.44	6.57
Mood Changes (Subjective Recording)	Increased Calm on Day 1; Increased Anger on Days 2-4	Increased Anger on Days 1-3
Headache	Reported on Days 1-2	No change
Fatigue	Reported on Days 1-2	No change
Nausea	Reported on Days 1-2	No change
Appetite Change	Decreased on Days 1-3	No change
Bowel Movement Changes	Increased bulk and movements on Day 1	No changes
Weight	No change	Decrease of 3kg over Days 1-7
Attention	Increased on Days 1-3	Not Reported
Metacognition	Increased on Days 1-5	Not Reported
Working Memory	Increased on Days 1-7	Not Reported
Changed Body Odour (Reflecting Donor Body Odour)	Reported on Days 1-7	Reported on Days 1-7

**Participants reported any effects experienced post-FMT for a 7 day period after the procedure. Effects reported after the female & male participant underwent an initial FMT procedure have been summarised in table 1.*

Table 2- Participant Experience 7 Days Post FMT After Repeated Procedure from Same Donor

Patient Experience 7 Days Post FMT, Second Procedure	
	Male Participant
Sleep (Average Hours Per Night)	6.43
Mood Changes	Increased Anger Days 1-7
Headache	No change
Fatigue	No change
Nausea	No change
Appetite Change	No change
Bowel Movement Changes	No change
Weight	No change
Attention	No report
Metacognition	No report
Working Memory	No report
Body Odour	Reported on Days 1-7

**Participants reported any effects experienced post-FMT for a 7 day period after the procedure. Effects reported after the male participant underwent a second FMT procedure have been summarised in table 2.*

Table 3- Fmt Healthy Participant Experiences Based On Qualitative Survey

FMT Participant Experience Based On Qualitative Survey		
Participant reported effect type & Duration	**Female Participant**	**Male Participant**
Body Odour	● Change in axillary odour, odour profile resembling that of FMT donor.	● Change in axillary odour, odour profile resembling that of FMT donor.
	● Changed odour most concentrated in axilla but also observed on skin surface.	● Changes not related to lifestyle (i.e. exercise, meals).
	● Changes not related to lifestyle (i.e. exercise, meals).	● Observations of changed body odour occurred daily immediately after FMT and regressed over time.
	● Observations of changed body odour occurred daily immediately after FMT and regressed over time.	● Changes still present 3 years post-FMT and continue to be observed once per week.
	● Changes still present 3 years post-FMT and continue to be observed once per week.	● Changed body odour observed most frequently immediately after a shower
	● Changed body odour observed most frequently immediately after a shower	
Immediately Post FMT	Yes	Yes
6 Months Post FMT	Yes	Yes
12 Months Post FMT	Yes	Yes
24 Months Post FMT	Yes	Yes
Mood	● Increased sense of calm & well being from immediately post-FMT	● Increased feelings of anger and intolerance experienced for 3 days post-FMT
	● Improved emotional control over baseline.	
	● Increased irritation, low frustration tolerance, poor emotional regulation days 2-4 post FMT.	
Immediately After FMT	Yes	Yes
6 Months Post FMT	No	No
12 Months Post FMT	No	No
24 Months Post FMT	No	No
Cognition	● Immediately post-FMT: poor attention control and other areas of weakness including metacognition of planning and cognitive and behavioural inhibition.	● No observed changes to baseline function
	● Immediately after FMT, profound, increased ability to attend to visual information for extended periods of time (i.e. reading)	
	● All effects felt immediately post-FMT with effects regressing over 7 days	
Immediately After FMT	Yes	Not Applicable

6 Months Post FMT	No	Not Applicable
12 Months Post FMT	No	Not Applicable
24 Months Post FMT	No	Not Applicable

**Table 3 presents changes experienced by the participants extracted from a qualitative survey. And establishes whether these effects were experienced at different intervals including immediately after FMT, 6, 12 and 24 months after FMT procedure.*

DISCUSSION

Body odour

Multiple novel outcomes were reported by both subjects during their experience post FMT. Of the unexpected changes, the most enduring effect reported by both participants was the change in body odour. Self-reported surveillance conducted by the subjects revealed that in the period post FMT they saw immediate changes in their body odour which reflected that of the donor and could not be attributed to cohabitation. Changes in body odour were most commonly observed in the axilla but detectable in all skin folds. These events were observed 6, 12 and 24 months post-FMT in both the male and female study subjects. While both subjects reported a regression in the frequency of observable occurrences of body odour events at 6 months post-FMT, it was also reported that enduring changed-body odour events continued to occur once per week 24 months post-FMT.

At the time of this case report, there appears to be no other record of patients or healthy volunteers that mention changes in body odour following FMT. However, while body-odour is largely attributed to local microbiota colonies on the skin, studies have mentioned the changes in gut health through the use of probiotics and diet manipulation have been used to treat a variety of skin disorders. This relationship has been termed the "gut-skin axis"[17,18]. Additionally, there is evidence that shows that differences in faecal microflora were observed in patients with skin pathologies compared with healthy control subjects[19] Despite this knowledge no studies have discussed the effects of FMT on body odour and warrants further investigation on the topic.

Studies have shown that gut microbiota interact with the reproductive endocrine system in women and that the gut microbiome has been allocated the status of an endocrine organ[20,21].

Previous studies have demonstrated that different levels of reproductive hormones are related to changed body odours[20,21,22]. As such, the findings regarding body odour in this case study could possibly be attributed to changes in endocrinology resulting from FMT altering gut microbiota.

Mood

Both subjects reported changes in mood immediately after undergoing FMT. Changes varied between subjects with the female subject reporting increased calmness on day 1 post-FMT followed by increased anger and intolerance on days 2-7 post FMT. The male subject reported increased feelings of anger on days 1-3 after his first FMT procedure and increased anger for days 1-7 after his second dose. Neither participant reported changes in mood after the first seven days post-FMT.

It has been acknowledged that the gut-brain axis has an effect on the human stress response and has been proposed as a potential treatment for psychiatric disorders related to stress[23].Multiple studies have explored the use of FMT specifically in the treatment of psychiatric disorders and have observed positive changes including a

reduction in stress, anxiety and depression[24]. However studies have also reported inverse results with psychiatric symptoms worsening post-FMT[24,25]. The findings in this case report support the notion that FMT has an impact on mood. The transient nature of these findings could relate to the FMT procedure itself rather than changed microbiome.

Cognition

Only the female participant reported changes in cognitive ability post-FMT. Prior to the procedure the female participant self-reported having areas of cognitive weakness in the executive functioning domains of attentional control and logical planning. Immediately following FMT the participant reported notable increases in the ability to attend visual information for extended periods (i.e. reading without distraction). The effects regressed over the seven day period post-FMT.

Current studies have documented that FMT can result in cognitive changes with some studies reporting improved cognitive outcomes for patients with certain pathologies such as hepatic encephalopathy & Alzheimer's disease. Though efficacy has varied between donor and recipient and recommended dosages have not been established. Differences in the microbiota of donor samples appeared to elicit differences in cognitive outcomes for participants[26,27]. The study by Bloom et al 2022 found that participants with the poorest cognitive outcomes had received their FMT sample from the same donor. This supports the documented importance of microbiota to cognitive function as described in the current literature.

A 2021 systematic review by Baldi et al analysed the modulation of gut microbiota and concluded that FMT may have the potential to enhance cognitive functions for both healthy subjects and patients with neurological pathologies. However it remains unclear whether the effects of FMT on cognition are cumulative or continuous[27].

Whilst mechanisms for improved cognition resulting from FMT are yet to be elucidated,
previous studies utilising animal models have confirmed the correlation between cognition and gut flora. Proposed mechanisms included metabolite regulation and alleviation of systemic inflammation[27,28,29] [30,31]. This evidence suggests that the cognitive changes reported by the female participant in this case study could be due to FMT however the mechanism by which this may have happened requires further investigation. Current evidence reports a number of metabolic changes that can result from FMT and proceed to enact changes in cognition via the gut-brain axis with exact mechanisms still to be clarified.

CONCLUSION

FMT has seen success in treating a range of GIT disorders. After these successes of FMT for GIT disorders and increased knowledge of the gut-brain axis, researchers have begun exploring other clinical applications for FMT. This case report presents the personal experiences of two healthy subjects undergoing exchange of FMT and novel short-term and long-term outcomes. The female participant reported immediate improvements in perceived area of cognitive weakness. These findings support the notion that FMT may have therapeutic applications for cognitive disorders. Limitations of this study include the lack of objective measures and reliance on self reporting their symptoms pre and post FMT accurately. Additionally a cohort of N=2 is not sufficient to draw significant statistical findings to validate any speculation.

Further studies should explore the effects of FMT on body odour and whether the mechanism by which this occurs relates to changes in local skin microbiome or could be attributable to endocrine changes influenced by the gut microbiome. Additionally, FMT should be tested in a larger cohort of healthy volunteers to explore extra-gastrointestinal effects including mood and cognitive changes and establish mechanisms by which these effects occur and if these effects are donor-specific. This case report supports current evidence that suggest FMT may have further effects that are extra-gastrointestinal in nature.

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