

ORIGINAL ARTICLE

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# Effects of education on health-related quality of life in multiple sclerosis patients at the Rabat and Casablanca region in Morocco

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## Abstract

**INTRODUCTION:** Multiple sclerosis is a neurodegenerative disease. It results in the deterioration in the health-related quality of life (HRQoL) of patients suffering from this pathology. This study examines the influence of level of education on the health-related quality of life of person with multiple sclerosis.

**METHODS:** The study was carried out on a sample of 90 multiple sclerosis patients. A questionnaire was used to collect sociodemographic and clinical data. Physical and mental health was assessed using the validated Multiple Sclerosis Patient Health-Related Quality of Life (MSQOL-54) and Patient-Determined Disease Stages (PDDS) questionnaires.

**RESULTS:** The mean age of the multiple sclerosis patients was  $35.17 \pm 1.07$ , the sex ratio was 3.09, and around 79% had reached university level. Moreover, the level of education was also associated with higher quality of life scores ( $p < 0.018$ ) with a highly significant difference between physical ( $p < 0.010$ ) and mental ( $p < 0.001$ ) health scores.

**CONCLUSION:** The implications of these results are discussed, highlighting the importance of access to education in the management of multiple sclerosis and improving patients' quality of life.

## INTRODUCTION

The orbitofrontal cortex (OFC) is accountable for a range of cognitive processes, encompassing sensory integration, decision-making, and the establishment of associations between stimuli and rewards. In the context of the aforementioned function, it is postulated that the orbitofrontal cortex (OFC) is associated with a pleasurable reaction to sensory input, particularly in relation to taste stimuli (Minematsu *et al.* 2018; Rudebeck & Rich 2018).

The cognitive processes involved in discerning and differentiating between enjoyable and aversive tastes play a crucial role in the identification of suitable food sources and the regulation of food consumption. Recent research utilizing near-infrared spectroscopy (NIRS) in this particular domain has uncovered that the hemodynamic responses of the medial orbitofrontal cortex (OFC) are influenced by the specific taste modality, such as bitter or sweet. The preceding research yielded a conclusion on the correlation between activity in the orbitofrontal cortex (OFC) and the subjective experience of pleasure associated with a particular flavor stimulus (Minematsu *et al.* 2018; Okamoto & Dan 2007).

At the behavioral level, individuals are typically categorized into three phenotypes: individuals with a strong preference for sweetness, individuals with a moderate like for sweetness but not intense sweetness, and individuals who dislike sweetness and exhibit a decrease in preference as sweetness increases (Iatridi *et al.* 2019). It is postulated that the diverse range of reactions to different sugary stimuli may also manifest in the neurological response to such stimuli, particularly in the orbitofrontal cortex (OFC). Witherly *et al.* (1980) postulated that individuals exhibit four distinct patterns of response to different sweetened beverages. These patterns can be characterized as follows: an initial increase in liking with higher concentrations of sweeteners, followed by a subsequent decline; a rise in liking, followed by a plateau (referred to as Type II); a continuous decrease in liking (Type III); and a non-linear change in liking (Type IV). Previous research on sensory perception has provided evidence to support the idea that reaction patterns to sucrose solutions can be categorized into four distinct shapes: positive slope, horizontal (or "flat") slope, inverted U-shape, or negative slope. Nevertheless, prior neuroimaging investigations have not specifically examined the response of the orbitofrontal cortex (OFC) to hedonic stimuli of varying intensities.

However, Minematsu *et al.* (2018) utilized various taste substrates; however, the examination of the relationship between reactions and concentration was not explored. The available research does not provide a definitive understanding of the unique and exclusive relationship between the orbitofrontal cortex (OFC) and the hedonic component of the reaction. These factors prompted the development of a paradigm that

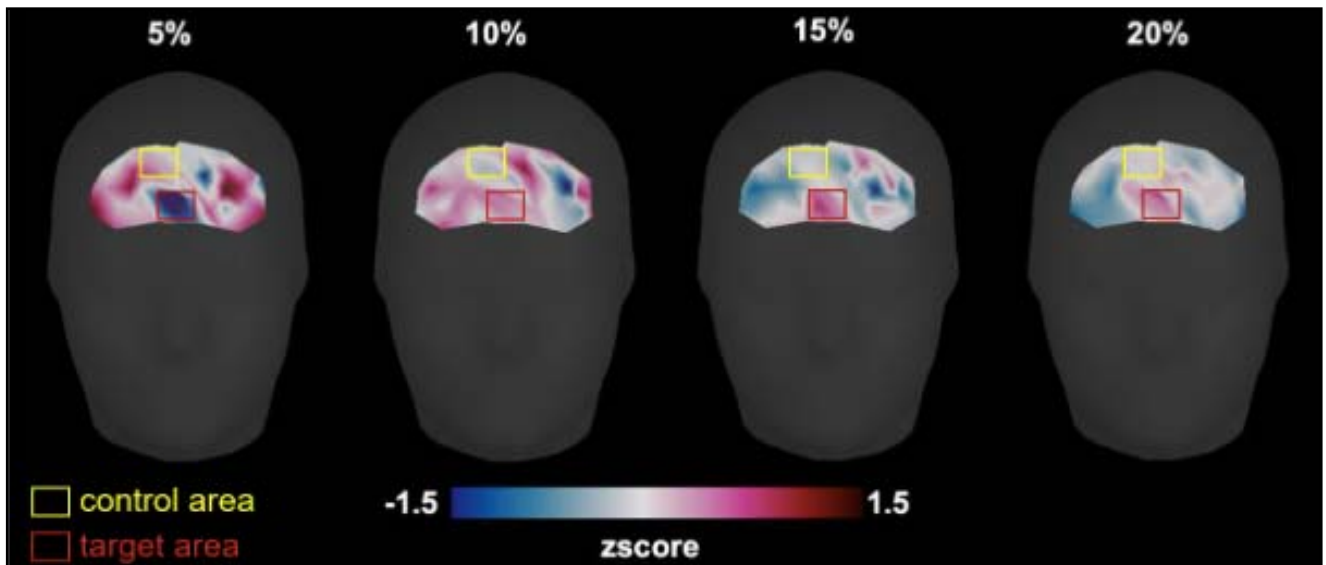
closely resembles the one previously mentioned, but with a focus on investigating the relationship between the concentration of sweet substances and reactions in the orbitofrontal cortex (OFC). Our hypothesis posits that if the response of the orbitofrontal cortex (OFC) indicates a hedonic reaction to a sweet stimulus, then an excessively sweet stimulus should not elicit a hedonic response in the OFC. Consequently, we expect to observe an inverted U-shaped pattern of OFC response, ranging from neutral to extremely sweet stimuli, in terms of hedonic pleasure. In an alternative scenario, if the reaction of the orbitofrontal cortex (OFC) is directly proportional to the strength of the stimulus, specifically in terms of sweetness (i.e., a sweeter stimulus elicits a stronger response), the most prominent OFC response will be observed when the sweetest stimulus is provided. We also hypothesized that if the OFC encodes hedonic pleasure, the individual OFC responses would be proportional to the individual pleasantness scores.

## MATERIALS AND METHODS

We implemented an Experiment 1 protocol modification from Minematsu *et al.* (2018) with the purpose of conducting a direct comparison between data obtained from previous research conducted by international colleagues and new observations. In the course of the study, a decision was made to replace the utilization of sucrose with fructose due to several factors. Firstly, there exists a potential risk that the sample population may include individuals with undiagnosed diabetes, which could result in an unfavorable reaction and potential harm. Secondly, fructose possesses a considerably higher level of sweetness compared to sucrose, thereby necessitating lower concentrations of the substance. Lastly, unlike sucrose, fructose does not provide direct energy value and induces a lesser degree of satiety, which holds significance when multiple stimuli are administered consecutively. Additionally, to reduce variability associated with swallowing, participants were instructed to hold the solutions in the mouth for a fixed duration before expelling them.

The research utilized a linear progression in the concentration of the solution, specifically at 5%, 10%, 15%, and 20% by weight. The solutions were prepared using distilled water and dried fructose powder. The weights of the solutions and the solutions themselves were determined just before the commencement of the experiment in order to mitigate the potential impact of water evaporation on the concentration of the prepared solution and its degradation as a result of natural factors. The solutions were maintained at an ambient temperature of  $23 \pm 2$  degrees Celsius.

In selecting stimulus concentrations, we referred to prior psychophysical research indicating that fructose is perceived as sweeter than sucrose by a factor of approximately 1.6 to 1.9 when both are dissolved in



**Fig. 1.** Topographical maps of the average HbO response during the 5–14 s interval.

distilled water at equal mass concentrations (Cardello *et al.* 1979). While more recent studies (e.g., Low *et al.* 2017; Mouillot *et al.* 2019) have noted that sweetness perception can vary depending on whether solutions are matched by mass or molarity, we chose to base our comparison on equal mass concentrations (g/100 mL), consistent with the Cardello *et al.* approach and common practice in sensory research. This rationale informed our inclusion of 5% fructose as roughly equivalent in perceived sweetness to 10% sucrose, although we acknowledge that precise equivalence may differ by individual. Future studies will include equimolar comparisons and separate subjective ratings of sweetness intensity and hedonic value to improve interpretive accuracy.

Disposable syringes and tubes were utilized for the purpose of regulating the administration of stimuli. The stimulus volume was constrained to 8 milliliters. The participant administered the stimulus by manually activating the syringe, thereby excluding the experimenter from the room and minimizing the potential for extraneous recording artifacts such as motor and light interference. Moreover, a controlled delivery of the stimulus was preferred to avoid any potential discomfort or unexpected reactions, including the risk of choking.

The examination was segmented into three distinct phases. Upon receiving a cue from the experimenter, the participant proceeded to ingest a liquid substance, retaining it within their oral cavity for the duration of 20 seconds. Following the expulsion of the liquid, the subject proceeded to cleanse their oral cavity with water in order to eliminate any remaining remnants of the sample. Upon the conclusion of the experiment, the participant employed a seven-point Likert scale to assess the palatability of the sample, with a rating of 1 denoting a severely unpleasant taste and a rating of 7 denoting an exceedingly enjoyable flavor. The

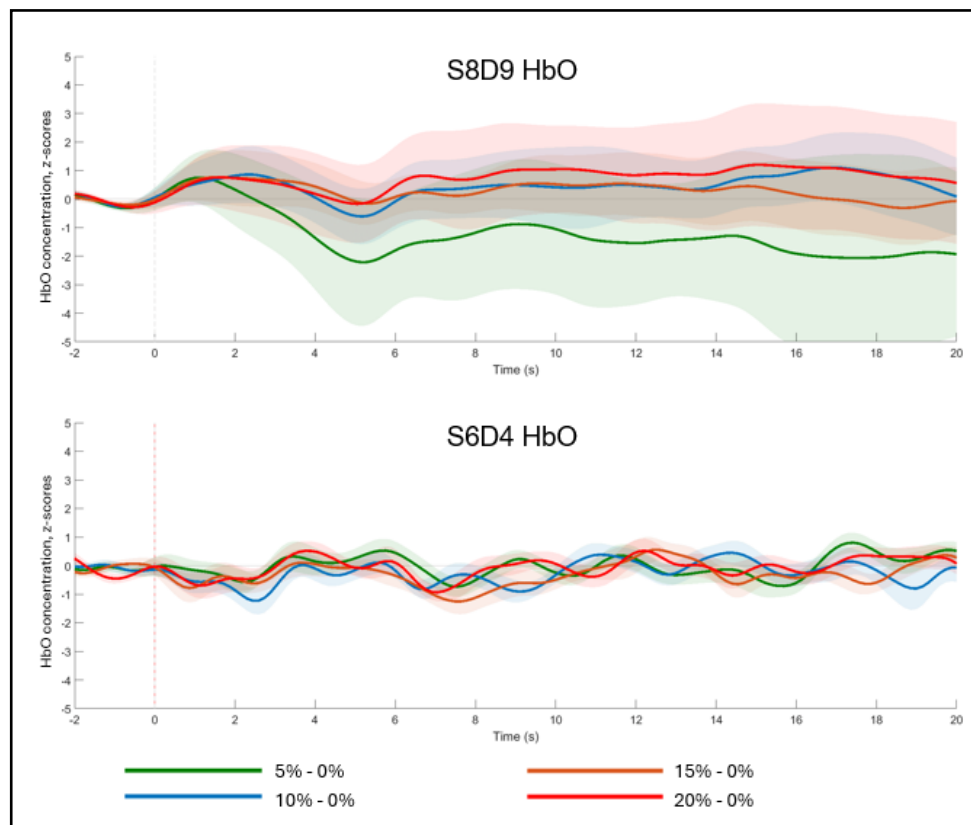
samples were dispatched in the subsequent sequence: the experiment involved the use of distilled water solutions with concentrations of 5%, 10%, 15%, and 20%. The aforementioned method was repeated on three separate occasions in order to mitigate the risk of data loss in the event of any potential inaccuracies in the recorded samples. The duration of the experiment encompassed around one hour, which encompassed the installation of optodes and the execution of calibration procedures.

To initiate the experiment, the participant engaged in a concurrent action of pulling the syringe plunger while simultaneously pressing the key with their other hand, thereby activating the trigger mechanism for data recording. After the initial trigger, the computer system promptly recorded an end mark 20 seconds later. Subsequently, the subject was notified of the test's conclusion and given the chance to provide their solution. The duration allocated for oral rinsing was theoretically boundless, although conventionally restricted to a period of 30 seconds.

#### fNIRS

The montage created employed a total of 9 sources and 9 receivers, resulting in a cumulative count of 35 leads. The distance between the source and receiver pair was measured to be  $3 \pm 0.3$  cm. The signal's sampling frequency was configured at 6.94 Hz. The light sources utilized in the experiment had wavelengths of 785 and 830 nm. This selection of wavelengths facilitated the differentiation between oxygenated and deoxygenated hemoglobin vibrations, since it caused distinct alterations in the absorption spectra.

To approximate coverage of the medial orbitofrontal cortex (mOFC), we positioned the sensor cap as low as anatomically feasible, lowering it approximately 0.5–1 cm below the standard 10–20 EEG placement.



**Fig. 2.** The superposition of evoked response curves, specifically the hemoglobin oxygenation (HbO) response, is observed in leads D9S8 and S6D4. Green, blue, orange and red – difference curve of 5%, 10%, 15%, 20% solutions and water.

Specifically, the S8D9 channel was located on the lower forehead, just below the AFp1 and AFp2 electrode positions (Oostenfeld & Praamstra 2001). This positioning is consistent with previous fNIRS studies targeting anterior mOFC, such as those by Minematsu *et al.* (2018) and Jeong and Yuan (2017), who demonstrated reliable detection of orbitofrontal activation using optodes in similar lower-frontal locations.

While fNIRS is limited by its penetration depth (~30–35 mm), prior modeling studies (e.g. Strangman *et al.* 2013; Eggebrecht *et al.* 2012) have shown that anterior and ventromedial prefrontal cortex structures—including the mOFC—can contribute detectable signals, particularly when using source-detector separations of 30 mm or greater. The light propagation follows a curved path, which allows sampling from intermediate depths. Therefore, although signals from more superficial frontopolar areas likely contribute to the measurements at D9S8, it is plausible that deeper sources, including the anterior mOFC, are also reflected in our data.

### Participants

A total of 23 healthy individuals, consisting of 16 females aged 21 years and older, had actively engaged in the primary stage of the research (present pilot study). All subjects were Caucasians, none of them reported following any strict food diet or having eating disorders or allergies. The collected data were processed, and two individuals were excluded due to an error in

the standard NIRX script that caused the data format to be altered (specifically, an exception occurred due to missing metadata). In this study, we did not use a screening questionnaire to distinguish sweet-likers or dis-likers, but the individual pleasantness scores obtained during the experiment showed no strong positive or negative dynamics in response to sweet intensity intensification.

The study protocol was approved by the local university ethics committee. Prior to participating in the trial, all participants provided written informed consent.

### Data analysis

The preprocessing of data involved conducting a visual examination of the data in order to identify any artifacts that may be peculiar to the methodology used. The identification of artifact eras was conducted, however later investigations did not utilize them. The proportion of such artifacts was around 1% of the total quantity of epochs, suggesting a significant level of preparedness within the paradigm for comprehensive documentation.

The raw labeled data underwent filtration using a bandpass filter spanning the frequency range of 0.01–0.5 Hz. This filtering process effectively eliminated any artifacts originating from the cycles of heart-beat, respiration, and blood pressure. Subsequently, the unprocessed data, which encompassed measurements of light intensity detected by the sensor, underwent analysis utilizing the adapted Beer-Lambert equation. This analytical process yielded the determination of the

relative concentrations of oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HbR), and total hemoglobin (HbT) (Herold *et al.* 2018).

The acquired recordings were segmented into epochs according to the nature of the event and were synchronized with the onset of the gustatory stimulus. The duration of the period was 32 seconds, with a relative offset of -2:30 seconds in relation to the stimulus. In order to mitigate the impact of channels with relatively high levels of noise in situations where there are just a few epochs, the data underwent standardization with respect to the prestimulus period using z-score standardization, which is a common procedure in this field.

In order to assess the overall result, the epochs were averaged based on the type of occurrence, namely five distinct categories of stimuli.

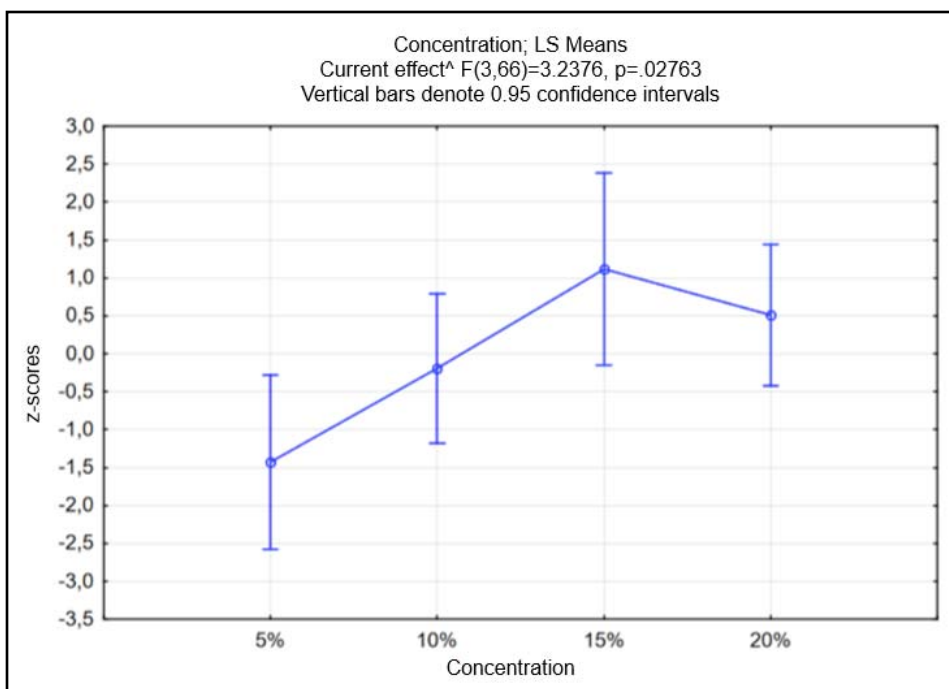
## RESULTS

In accordance with previous research (Minematsu *et al.* 2018), the reaction elicited by the distilled water stimulus was utilized as a reference point and subtracted from the response induced by the sweet solution stimulus for subsequent analysis. The sensor that received information from the medial orbitofrontal cortex (D9S8) was selected for the initial round of statistical analysis, following also with the nearest sensor S6D4 that was located approximately 4 cm above the target sensor. We included S6D4 as a control site to assess the regional specificity of orbitofrontal cortex (OFC) responses. Although located approximately 4 cm superior to D9S8, the S6D4 channel covers a distinct cortical region. Based on optode placement aligned to the 5–5 EEG system, S6 corresponds approximately to the F2 electrode, and D4 to AFz, placing S6D4 over the

right anterior dorsolateral prefrontal cortex (DLPFC) (Oostenveld & Praamstra 2001). The DLPFC is functionally associated with executive control and working memory, rather than gustatory or hedonic processing (Miller & Cohen 2001; Petrides 2005). As such, we did not expect this region to show concentration-dependent modulation. Indeed, while D9S8 exhibited a graded hemodynamic response to increasing sweetness, S6D4 did not, consistent with previous findings on the functional role of the OFC in encoding hedonic value (Rolls 2011; Small *et al.* 2007). These contrasting patterns support the functional dissociation between regions and validate the use of S6D4 as a control channel in this study.

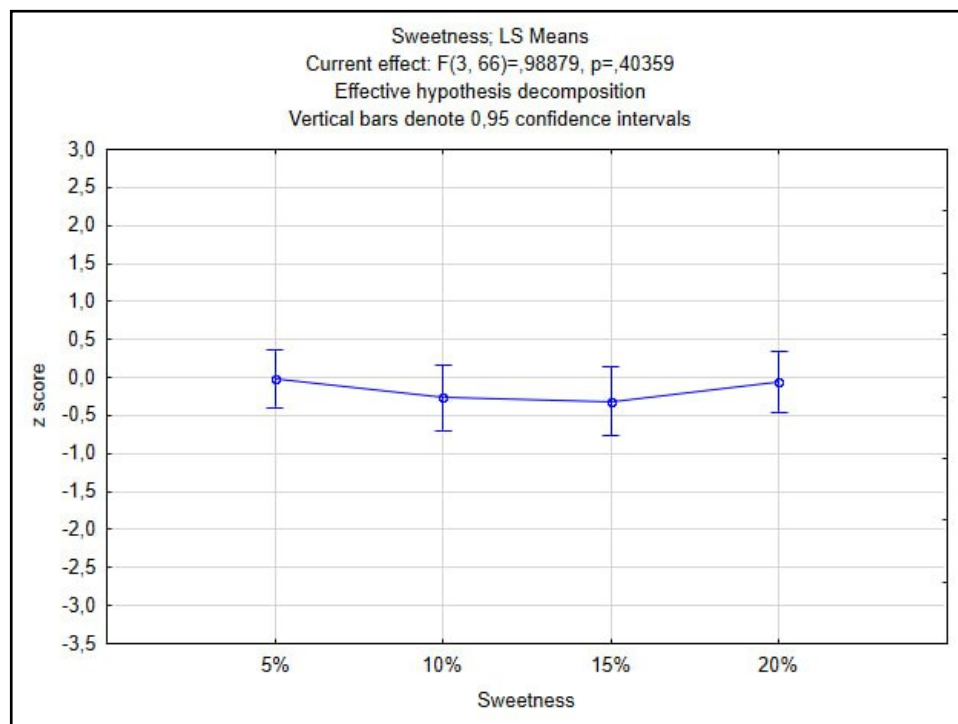
Topographical maps of the average HbO response during the 5–14 s interval are presented in Figure 1. The curves produced from the experiment indicate a likely positive correlation between the strength of the response and the concentration of the solution (Fig. 2). The utilization of the oxygenated hemoglobin concentration curve as a correlate of the metabolic response was based on its higher sensitivity to brain tissue activity compared to deoxygenated hemoglobin concentration. The averaging of the data for lead D9S8 in the 5–14 s range was conducted for the purpose of analyzing variance, due to the delayed nature of the hemodynamic response. In order to accommodate for variations among individuals, the mean of all amplitudes for each participant was calculated and subsequently subtracted from each individual data point.

In order to establish a connection between behavioral reactions and hemodynamics, we employed a Spearman correlation test. This test allowed us to examine the relationship between scores representing behavioral responses and the amount of hemodynamic



**Fig. 3.** Results of ANOVA analysis on sensor D9S8; x-axis represents solution concentration, y-axis - amplitude of normalized responses to stimuli.





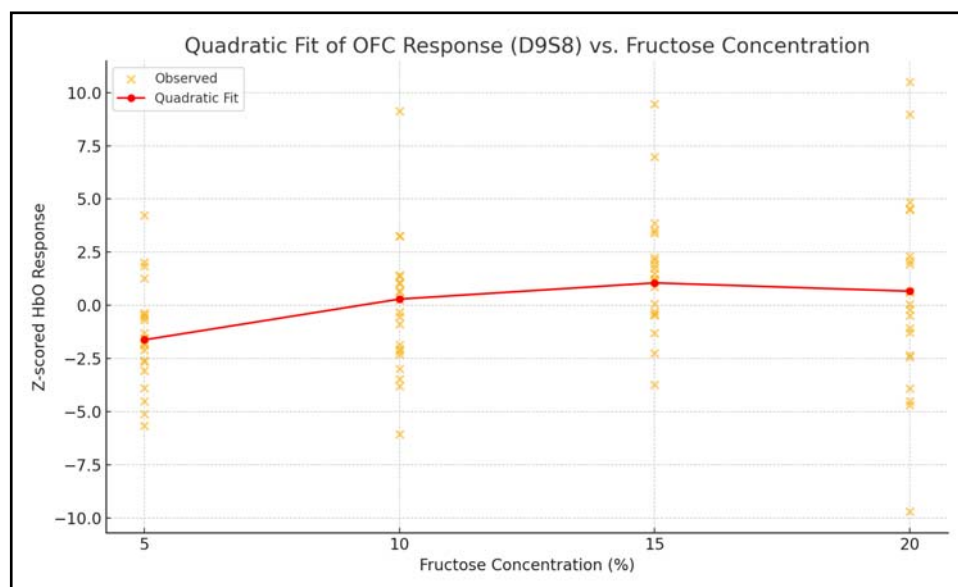
**Fig. 4.** Results of ANOVA analysis on sensor S6D4; x-axis represents solution concentration, y-axis - amplitude of normalized responses to stimuli.

responses observed during a specific test. To assess individual variability in hedonic response, we also analyzed pleasantness ratings across all concentrations and found no consistent monotonic trends, suggesting the absence of extreme sweet-liker or dis-liker profiles within the current sample ( $F(3, 60) = 1.73, p = 0.17$ ). In order to accommodate for individual differences, the average of all scores for each subject was computed and subsequently subtracted from each individual score.

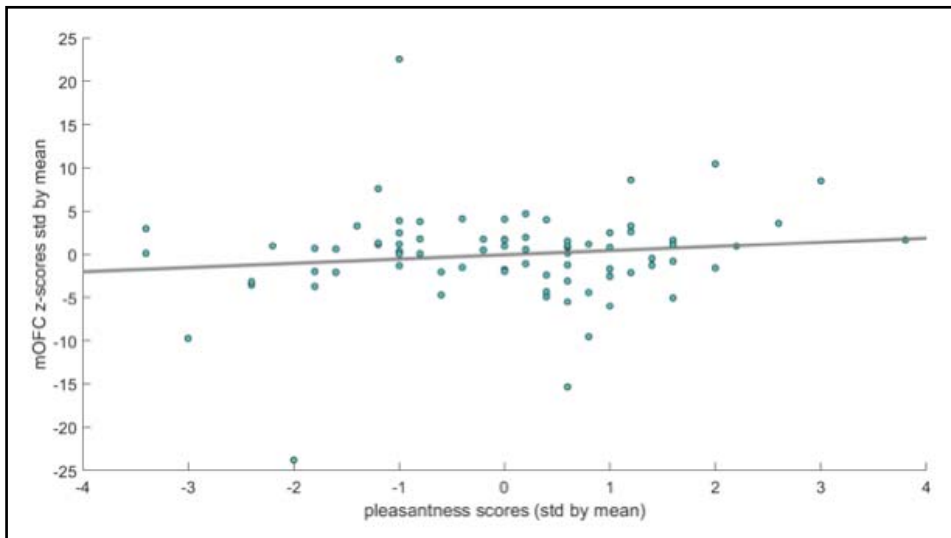
The statistical analysis employed was rmANOVA, which yielded significant results for the factor Concentration ( $F(3, 66) = 3.2376, p = .02763, \eta^2p = 0.13$ ). The results could indicate that as the level of sweetness

increased, there was a corresponding rise in the magnitude of reactions. Further exploration with extended sample size is needed to show reproducibility of these results. Statistical analysis using Fisher's post-hoc test revealed significant differences between the 5% and 15% fructose solutions (with an amplitude difference of -1.43 compared 1.12,  $p < 0.01$ ), as well as between the 5% and 20% fructose solutions (with an amplitude difference of -1.43 versus 0.51,  $p < 0.03$ ) (see Fig. 3). The same analysis was replicated for the sensor S6D4 (see Fig. 4) ( $F(3, 66) = 0.99, p = 0.40$ ).

To formally evaluate the hypothesized non-linear response pattern of the orbitofrontal cortex (OFC) to



**Fig. 5.** Results of second-order polynomial regression analysis on the normalized HbO responses from channel D9S8.



**Fig. 6.** Relationship of the amplitude of the hemodynamic response (y-axis) and the behavioral assessment of the pleasantness of the stimulus (x-axis).

increasing concentrations of sweet stimuli, we conducted a second-order polynomial regression analysis on the normalized HbO responses from channel D9S8 (see Fig.5). The model included linear and quadratic terms for concentration. While the overall regression model reached statistical significance ( $F(2, 81) = 3.86$ ,  $p = 0.025$ ), the quadratic term itself was not statistically significant ( $\beta = -0.023$ ,  $p = 0.123$ ). The negative coefficient suggests a potential inverted U-shaped pattern; however, the evidence was not sufficient to confirm a non-linear trend in the current dataset. This may be due to the limited number of concentration levels ( $n = 4$ ) and the sample size. Despite the lack of statistical support for non-linearity, the observed attenuation of the response at the highest concentration (20%) is consistent with the proposed hedonic tuning hypothesis and motivates more fine-grained testing in future research.

The results of the correlation analysis (see Fig. 6) indicated that there was no statistically significant association between behavioral reactions and the magnitude of changes in hemoglobin concentration ( $R = 0.12$ ;  $p = 0.26$ ). However, we cannot deny that the data had a moderate tendency to significant positive correlation, leading to an assumption that the collected sample had not enough statistical power to detect relatively small effects.

To illustrate the trials' consistency, we calculated a series of correlation analyses on fNIRS data. We chose S8D9 HbO source (the target area), and for each condition and each subject ran a Pearson correlation analysis between mean HbO curves and each trial earning 3 r-scores per condition for each subject in 0 to 20 s time window. Then, we averaged the r-values across subject that resulted in one mean r-value per subject per condition. In all conditions, the mean r-value was higher than 0.7 for most of the subjects, and no less than 0.55 for all of them, which confirms reliability in the neural measures in our study

## DISCUSSION

The findings of our pilot investigation provide evidence in favor of the hypothesis positing a direct association between the metabolic response of the medial orbitofrontal cortex (OFC) and the perceived sweetness of the stimulus. The findings indicate that the reaction to a moderate level of sweetness stimulus is significantly less pronounced compared to the reaction to an excessive level of sweetness stimulus. Additionally, there was no observed correlation between an individual's subjective experience of taste pleasantness and the magnitude of hemodynamic responses in the medial orbitofrontal cortex (OFC). This study is best understood as a psychological investigation, as it centers on how subjective cognitive and emotional processes—specifically the perception of sweetness and its hedonic evaluation—influence and are reflected in brain activity. The orbitofrontal cortex (OFC), a region implicated in reward, decision-making, and emotional appraisal, was examined here in the context of individual differences in taste perception. By measuring both self-reported ratings and neurophysiological responses, the study bridges behavior and brain function—two fundamental domains of psychological science. Moreover, the study probes how internal psychological constructs, such as "pleasantness," vary across individuals and interact with sensory input, which is a classic psychological question grounded in cognitive and affective neuroscience.

The confluence of the two analyses raises doubts regarding the assertion that activation of the orbitofrontal cortex (OFC) is rooted in hedonic processes under the parameters of our experimental setup. The inclusion of such data greatly enhances our comprehension of the functional role played by the orbitofrontal cortex (OFC) in the process of food consumption, while also shedding light on theories pertaining to the connection between OFC activity and the manifesta-

tions of eating disorders (Rolls 2011, 2012; Small *et al.* 2007).

It is important to highlight, however, that the previous study (Minematsu *et al.* 2018) employed a sucrose solution, which is a disaccharide composed of glucose and fructose. Through the utilization of functional magnetic resonance imaging (fMRI), scholars have made a noteworthy observation about the impact of glucose and fructose intake on cerebral activity. Specifically, it has been found that fructose consumption elicits a comparatively reduced activation of the striatum. The establishment of comprehensive knowledge on the functional reactivity of the OFC in relation to different types of sweet substrates necessitates the consideration of such distinctions.

The HbO response tends to be negatively deflected for the 5% fructose solution, whereas very sweet solutions demonstrate positive deflection. The previous study utilized 10% sucrose solution. Since the fructose sweeter than sucrose by a factor of 1.6 – 1.9 (Cardello *et al.* 1979) in solutions of the same mass concentration, the 5% fructose solution should be comparable to the stimulus used in Minematsu *et al.* (2018). The observed response of the OFC demonstrates decrease of the HbO concentration which corresponds to the earlier reported results. However, stimuli with higher concentration of the sweetener demonstrated slightly negative (10%) or positive (15%, 20%) deflection, therefore, showing an inversion of the effect observed for the less sweet stimulus. If we state that the pleasant stimulus application leads to the decrease of HbO levels, the inverted response may be related to the displeasure caused by an uncomfortable level of sweetness. Minematsu *et al.* (2018) demonstrated a negative correlation between the pleasantness of the stimulus and HbO concentration which supports our results as well. Based on these observations, we implemented the research paradigms for our main study to collect information on both sweetness and pleasantness according to the participants' perception.

Given that each participant was exposed to three repetitions of the stimuli, future analyses using the full dataset ( $n > 40$ ) will include additional tests to examine whether hemodynamic responses vary systematically with the sequence of stimulation. This will allow us to investigate potential habituation or sensitization effects over time. Although our current pilot sample ( $n = 21$ ) did not yield statistically significant correlations between subjective ratings and OFC responses, we did observe a weak trend toward significance, particularly at mid-to-high concentrations. This suggests that the relationship between neural activation and perceived pleasantness may be subtle and subject to interindividual variability. It is plausible that the limited sample size in this preliminary phase reduced our power to detect small to moderate effects. To better understand individual variability in hedonic processing, we also plan to incorporate measures of participants' attitudes

toward and consumption of sweet foods in the next stage of data collection. This will enable us to explore how trait-level sweet preference and consumption behavior relate to the magnitude and dynamics of OFC responses. Together, these extensions aim to clarify the neural basis of hedonic evaluation and improve the interpretability of the observed patterns.

Our reported results demonstrated rather controversial results in terms of comparison with the previous study. On one hand, we observed no significant correlation between pleasantness scores and HbO deflection on the individual level but only a tendency to a positive relationship between the behavioral and physiological responses. On the other hand, mean post stimulus level of HbO across subjects demonstrated change from negative to positive scores with the growth of the fructose concentration which roughly corresponds to the previously reported negative correlation between the pleasantness scores and HbO levels (if we state that the very sweet solutions lead to displeasure of the participants). Moreover, another source of noise in our data can be related to the behavior of the subjects who can misinterpret "pleasantness" as "sweetness" that could lead to incorrect scoring during the experiment. These observations motivated us to correct the paradigm and ask the participants to score both sweetness and pleasantness to break the possible link between them to use in future studies.

A limitation of the current study lies in the spatial resolution and anatomical specificity inherent to surface-level fNIRS recordings. While standard optode placement allowed us to approximate activity in the medial orbitofrontal cortex (mOFC), signal contamination from adjacent prefrontal regions (e.g., frontopolar cortex) cannot be ruled out. In future iterations, we plan to implement source localization and anatomical coregistration techniques (e.g. via Atlas-Viewer or NIRSTORM) using individual or standardized MRI templates. These enhancements will allow for more accurate estimation of cortical activation patterns and help delineate contributions from distinct regions within the prefrontal cortex.

The results of this study will enable us to draw inferences regarding the correlation between the functional activation of the orbitofrontal cortex (OFC) in response to the consumption of sweets and an individual's specific behavioral characteristics. The present methodology exhibits promise for further use in the field of clinical investigation pertaining to eating disorders, particularly due to the comparatively lower cost and increased availability of the fNIRS technique in comparison to fMRI. Moreover, the fNIRS method provides crucial insights into the hemodynamic responses of the orbitofrontal cortex.

These findings contribute substantially to the current understanding of the specificity of the orbitofrontal cortex (OFC) in relation to sweet stimuli. Nevertheless, it is important to note that in prior experiments,



another type of sweetener was employed. Additional investigation is necessary to reconcile the discrepancies by conducting a comparative analysis of the orbitofrontal cortex (OFC) response to sucrose and fructose. In general, the results of this study hold academic importance in relation to the fundamental examination of the function of the orbitofrontal cortex (OFC), as well as its potential therapeutic implications within the field of eating disorders.

## CONCLUSION

The results suggest that individuals exhibit a diminished response to a moderate amount of sweetness stimulus in comparison to their response to an extreme degree of sweetness stimulus. Furthermore, no discernible association was found between an individual's subjective perception of taste pleasantness and the extent of hemodynamic reactions in the medial orbitofrontal cortex (OFC).

## AUTHOR CONTRIBUTIONS

AG and OZ contributed to the design. SA, AS, SZ and AK completed the data collection. AG and OZ analyzed the data. All authors contributed to the interpretation of the results and writing of the manuscript.

## DATA AVAILABILITY

Data will be made available on request.

## CONFLICT OF INTEREST STATEMENT

The authors have no financial interest in this manuscript and no competing interests to disclose.

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