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Human perception of coffee aroma and its odor-active molecules: role of the olfactory threshold and the *OBPIIa* gene

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ABSTRACT

The olfactory perception of the aroma of both foods and beverages and the individual molecules that compose them is influenced by the olfactory performance of individuals and the genetic factors that contribute to it. Among commonly consumed beverages, coffee is the most popular non-alcoholic one in the world, in accordance with its social significance and functional effects. Recent studies have identified the social and environmental factors that determine whether an individual is a coffee drinker or non-drinker. Knowing the key aroma compounds of coffee, identifying interindividual differences in the number and intensity of odor-active compounds and the factors involved, could be important to understand what guides consumers in their choice of whether or not to drink coffee. In this study, using the coupled Gas Chromatography-Olfactometry technique, the headspace components of roasted coffee beans were separated and evaluated by volunteers. Each participant, genotyped for the *rs2590498* (A/G) polymorphism of the *OBPIIa* gene, was asked to identify and provide a personal evaluation of the pleasantness and intensity of each odor molecule. The results showed that both the ability to perceive odor-active compounds and the intensity with which they are perceived are correlated with the olfactory threshold and the *OBP* genotype of individuals. The reported pleasantness for the coffee aroma was determined by the hedonic valence attributed to each molecule in terms of pleasantness/unpleasantness. These results could be of great interest to the coffee industry, providing useful information for the development of new blends. In fact, taken together, these findings suggest that the perception of coffee odor is highly subjective due to both physiological and genetic factors.

1. Introduction

The main functions of the olfactory system are oriented towards identifying danger signals, social communication and eating behavior (Croy et al., 2014; Stevenson, 2010). Regarding the role of smell in eating behavior, individuals use it to choose foods, and this is reflected in the composition and size of meals. Through the orthonasal perception of certain odors, the appetite for foods containing them is stimulated, while retronasal stimulation decreases the appetite not only for these foods, but also for others (Bolhuis et al., 2012; Ramaekers et al., 2014; Ruijschop et al., 2008; Yin et al., 2017). An altered sense of smell leads individuals to modify their food choices: these people prefer high energy foods (such as sugars and fats) because they are more gratifying than healthier foods such as fruits and vegetables. Besides, individuals tend to add salt and spices to enhance the flavor of what they eat, thus increasing its rewarding power, which is instead reduced by a lower olfactory sensitivity (Aschenbrenner et al., 2008; Connor et al., 2018; Duffy et al., 1995; Gaillet-Torrent et al., 2014; Islam et al., 2015; Manesse et al., 2017; Postma et al., 2019; Velluzzi et al., 2023).

Most food and beverage odors are blends of molecules, which means that some odors can be masked by others and therefore not perceived, thus preventing access to the information they contain. It has been reported that the smell of the strongest compound(s) prevails in the blend and determines its overall odor (Ferreira, 2012a, 2012b). Pleasant odor-masking compounds could make a food smell unpleasant, while the inability to perceive unpleasant odors could make it more pleasant and acceptable to individuals.

Coffee is the most popular non-alcoholic beverage in the world, consistent with its social significance and its functional effects (Esquivel & Jiménez, 2012; Samoggia et al., 2020; Shen et al., 2023). From a social point of view, coffee consumption is seen as a break from work activities, a socializing factor, and an integral part of the people's lifestyle

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(Angeloni et al., 2021; Carvalho et al., 2015; Dórea & da Costa, 2005; Mundel et al., 2017; Samoggia et al., 2020; Samoggia & Riedel, 2018). From a functional perspective, coffee can prevent chronic diseases such as cancer, prevent or alleviate neurodegenerative diseases such as Parkinson's and Alzheimer's, prevent cardiovascular disorders and alleviate hypertension, and have antiadipogenic, antidiabetic and neuroprotective effects (Hu et al., 2019; Kusumah & Gonzalez de Mejia, 2022; Ludwig et al., 2014; Shen et al., 2023; Silva et al., 2022; Socała et al., 2021; Yao et al., 2022).

Recent studies have focused on understanding the factors that drive individuals to be coffee drinkers or non-drinkers. Quality, flavor and ethics were the primary drivers of consumption and, with the new century, the act of drinking a coffee beverage has evolved. It includes several mixed factors, such as pleasure, experience, lifestyle, and social status (Kanjanakorn & Lee, 2017; Samoggia et al., 2020; Samoggia & Riedel, 2018). Sensations of energy, gratification and pleasantness are among the reasons that drive individuals to consume coffee, while taste and fear of coffee's health impacts are among the reasons that make an individual a non-consumer (Samoggia et al., 2020). Coffee is appreciated and loved mainly for its unique sensory properties, which include an intense and full-bodied aroma, a bitter/acidic taste and a pleasant aftertaste (Angeloni et al., 2018; Angeloni et al., 2021; Buratti et al., 2017).

Using the gas chromatography technique it is possible to separate the molecules that compose the complex odor of a food and, by coupling it with an olfactometer (an olfactory evaluation device that uses the human nose as a detector), it is possible to evaluate the contribution of the odor of each single component to the overall aroma, that is, the subjective response of how each single compound is perceived by individuals (Brattoli et al., 2013; Delahunty et al., 2006; Schilling et al., 2010). Recently, several studies were aimed to identify odor-active compounds within a blend (i.e. compounds that are smelled by the human nose) and the characteristics of their perception, in order to improve the quality of flavored products, such as foods and beverages, by identifying natural and/or synthetic compounds that make them more pleasant and desirable to consumers (Brattoli et al., 2013; Crnjar et al., 2023; Nuzzi et al., 2008; Sollai et al., 2020). Knowing the key compounds of coffee aroma and identifying inter-individual differences in their perception could be important for understanding what drives people to drink or not drink coffee.

The perception of odorants begins with their binding to the olfactory receptors (ORs), located in the ciliary membrane of the olfactory sensory neurons, which in turn are immersed in a thin layer of mucus rich in water and glycoproteins (Breer, 1994; Pelosi, 1996). Since most odorant molecules are lipophilic and poorly soluble in aqueous environments, an important role appears to be played by odorant binding proteins (OBPs), which are particularly abundant in olfactory mucus. Indeed, one of the main functions of these proteins is to act as carriers for odorants, transporting the odorants close to the receptor site of ORs (Archunan, 2018; Biessmann et al., 2010). Previous studies have shown that the *rs2590498* (A/G) polymorphism of the gene encoding human *OBPIIa*, the only OBP found in the olfactory mucosa of humans (Briand, 2009; Silva Teixeira et al., 2016), plays an important role in the interindividual variability in the olfactory perception of simple and complex odors. In particular, subjects homozygous for the major allele A show better olfactory performance than subjects heterozygous or homozygous for the minor allele G (Melis et al., 2021; Sollai et al., 2019; Sollai et al., 2022).

Given the increase in coffee consumption over the past 20 years, the social and functional significance this beverage has in people's lives, and considering that most studies on the olfactory properties of coffee have evaluated the blend's complex aroma and how its odor can influence individuals' attention span and appetite, the primary objective of this study was to investigate the role of individual olfactory thresholds in the perception of the molecules that make up the coffee blend. First, we tested the effect of the *rs2590498* (A/G) polymorphism of the human gene encoding *OBPIIa* on participants' olfactory thresholds, on the number of aroma-active compounds, and on the average intensity perceived by each individual. Second, we assessed the correlation between perceived intensity of coffee aroma and perception of single compounds, and the effect of the *OBP* polymorphism on the perception of coffee aroma. Finally, we studied the pleasantness or unpleasantness with which aroma-active compounds were perceived and their contribution to the evaluation of the hedonic valence of coffee aroma.

2. Materials and methods

2.1. Subjects

Volunteers (41 F, 40 M, age 18–56 years, BMI 18.5–24.99 Kg/m2) were recruited through a public call at the University of Cagliari. On the day of the experiment, each volunteer was asked not to use perfumes and to fast for at least 1.5 h before starting the olfactory tests. Each participant was asked to sign an informed consent form and read the experimental protocol approved by the local ethics committee (Prot. PG/2021/14278, 22.09.2021). The following inclusion criteria were applied in selecting the volunteers: healthy individuals, non-smokers, with a good sense of smell (subjectively assessed) and familiarity with the coffee aroma. However, individuals with chronic pathologies such as inflammatory/autoimmune, neurodegenerative, cancer, metabolic, cognitive, cardiovascular and respiratory diseases were excluded (Aydın et al., 2016; Besser et al., 2020; Chamberlin et al., 2024; Jacobson et al., 2024; Kouzuki et al., 2018; Potter et al., 2020; Ross et al., 2008; Sollai et al., 2021; Wang et al., 2025).

2.2. Olfactory sensitivity screening

The threshold olfactory function of the participants was assessed using the threshold test, one of the sub-tests of the Sniffin' Sticks battery (Burghart Instruments, Wedel, Germany) (Hummel et al., 1997). To determine the olfactory threshold, the experimenter was given 16 triplets of pens (16 increasing concentrations). Each triplet consisted of two pens containing a solvent, while the third (target pen) was filled with the test odor (n-butanol). The participant's task was to identify the pen containing n-butanol. The concentration began at a very low level and increased until the participant identified the target pen twice in a row. This is the starting point and represents the first reversal. Subsequently, the order was decreased by one triplet until the participant made an error, at which point the order was increased (second reversal), and so on for seven reversals. The olfactory threshold was defined as the average of the dilution steps of the last four reversals. Each triplet is presented at approximately 20-s intervals. The score assigned to each participant ranges from 1 to 16.

To evaluate the intensity and pleasantness of the coffee aroma, each participant was asked to rate on a scale called the "Visual Analogue Rating Units" (VARUs), the intensity (score 0–20) and the perceived pleasantness (negative score from −1 to −10; positive score from 1 to 10) for the complex coffee aroma contained in pen #10 (hereafter referred to as coffee-odor pen) of the Sniffin' Sticks battery identification test (Fischer et al., 2014; Sollai et al., 2020).

2.3. Genetic analysis

DNA was isolated from 2 mL of unstimulated whole saliva using the QIAamp® DNA Mini Kit (QIAGEN S.r.l., Milan, Italy), following the manufacturer's protocol. DNA yield and purity were evaluated by measuring the absorbance at 260 nm using a NanoDrop One Spectrophotometer (Thermo Fisher Scientific). Subjects were genotyped for the *rs2590498* (A/G) polymorphism of the *OBPIIa* gene using a customized TaqMan® SNP Genotyping Assay (code: 4332077, Applied Biosystems by Life-Technologies Italia, Europe BV), as previously described (Sollai et al., 2019; Tomassini Barbarossa et al., 2017). PCR amplification was carried out using two primers: sense primer-GCCAGGCAGGGACAGA

and antisense primer-CTACACCTGAGACCCCACAAG. Two allele-specific TaqMan probes were created: VIC-labeled probe: TCGGTGACATGAACC and FAM-labeled probe: TCGGTGACGTGAACC. PCR reactions were performed in 96-well plates under fast thermal cycling conditions. Each reaction mixture contained 10 ng of DNA, 1X TaqMan® Genotyping Master Mix (code: 4371355), 1X TaqMan® Genotyping Assays and nuclease-free water. Amplification and fluorescence detection were performed using the StepOne™ Real-Time PCR System, while genotype assignment was achieved by allelic discrimination analysis with Sequence Detection Software (Genotyping module, Applied Biosystems, version 2.3; Life Technologies Italia, Monza, Italy). All samples were analyzed in duplicate, and both positive and negative controls were included in each plate. Molecular analyses revealed that 25 subjects were homozygous AA, 16 were heterozygous AG and 40 were homozygous GG.

2.4. Dynamic headspace sampling

The dynamic headspace extraction was used to collect compounds from roasted coffee beans (Nuzzi et al., 2008; Rizzolo et al., 1992). The headspace method allows obtaining an extract, whose volatile composition is directly correlated with the aroma quality assessed by the user (van Den Dool & Kratz, 1963).

Furthermore, the extracts thus obtained can be used both for analysis with a mass spectrometer coupled to a gas chromatograph (MS-GC analysis) and for sensory evaluation by a human assessor (GC-O analysis) (Nuzzi et al., 2008).

A 0.5 L airtight glass tank with a flow-through mechanism was filled with approximately 100 g of roasted coffee beans (Crnjar et al., 2023). The volatile-laden air was then directed into a glass tube (Ø 5 mm) containing a Porapak Q filter (150/75 mg, 50/80; Supelco) placed in the vessel's top collection port. The volatiles were recovered at room temperature after flushing the system with purified air for three hours at a rate of 30 L/h (500 mL/min). A solution containing the separated volatiles was obtained by releasing the trapped volatiles from the Porapak Q tube using 1.5 mL of 1-hexane. The samples were then stored at −20 °C until use. Three GC runs were performed 24 h after sample preparation to confirm the efficacy of the extracted material and the reproducibility of the chromatogram. The validity of the headspace was demonstrated by the fact that the chemical profile was consistent with that of previous studies (Crnjar et al., 2023; Sollai et al., 2024) and comparable to that from other studies (Akiyama et al., 2003; Caporaso et al., 2018; Gloess et al., 2018; Lee et al., 2017; López-Galilea et al., 2006; Majcher et al., 2013; W. B. Sunarharum et al., 2014b; Yang et al., 2016; Zapata et al., 2018).

2.5. Mass spectrometry/gas chromatography–olfactometry (MS/GC-O) analysis

To perform GC-O tests, we injected a 1 μL volume of coffee extract into the HP-INNOWax column (30 m × 0.25 mm × 0.50 μm; Agilent 19,091 N-233; Agilent technologies, Santa Clara, CA, USA) of the gas chromatograph (GC; Agilent 6890 N). This volume was split 1:1 between the olfactometry detection port (Gerstel ODP3; Gerstel, Mülheim an der Ruhr, Germany) and the mass spectrometer (MS) detector (Agilent 5973; Agilent technologies, Santa Clara, CA, USA) coupled to the GC (Sollai et al., 2020). The carrier gas was helium (1.2 mL/min). For the GC runs, we used the same protocol reported in previous studies (Crnjar et al., 2023; Sollai et al., 2020). The volatiles in our coffee extract were identified using the mass spectrum found in the MS Standard Library NIST2014 (US National Institute of Standards and Technology; Gaithersburg, MD, USA).

Each time a volatile substance was smelled, the participant recorded his/her individual rating of the perceived odor-active compound on a computer: intensity, duration, hedonic value and identification, using a digital recording and reporting system (GERSTEL ODP 3 for Windows 7) (Nuzzi et al., 2008; van Ruth, 2001). The identification reported by the participants was compared with the organoleptic information relating to the odor descriptors available on the Good Scents Company Information System (www.thegoodscentscompany.com) (Crnjar et al., 2023; Gonzalez-Kristeller et al., 2015). We have previously shown that 50 volatile compounds could be obtained from the headspace of roasted coffee beans: 48 of these molecules were perceived by at least two of the participants and are those to which we refer as “total-aroma compounds”; instead, 21 molecules are those indicated in the literature as having a coffee odor and only 19 of these were identified by the participants as “coffee-aroma compounds” (Crnjar et al., 2023; Sollai et al., 2024). The samples were presented blind to avoid expectation biases. The method we chose to assess each participant's ability to perceive single compounds during GC-O experiments is the detection frequency method, as it represents interindividual variability and does not require expert evaluators (Acampora Zellner et al., 2008; Brattoli et al., 2013; Dussort et al., 2012; Plutowska & Wardencki, 2008; Pollien et al., 1997).

2.6. Statistical analysis

Correlation analyses were used to assess the relationship between; a) the olfactory threshold score and the number of total-aroma compounds (defined as olfactory active compounds regardless of odorous quality) and coffee-aroma compounds (defined as olfactory active compounds having a coffee odor) smelled by each participant, the average intensity reported for them by each participant, and the intensity referred for the coffee-odor pen, also based on their AA or AG/GG *OBPIIa* genotype; b) the intensity reported for the coffee-odor pen and the number of total-aroma compounds and coffee-aroma compounds perceived by each participant, and the average intensity reported for them; c) the hedonic value reported for the coffee-odor pen and that for each total-aroma compounds and coffee-aroma compounds perceived by each participant. Pearson's correlation or Spearman's correlation test were used, respectively, depending on whether the normality assumption was met. Statistical analyses were performed using GraphPad Prism (Version 8.1; GraphPad Software, San Diego, CA, USA). A statistically significant correlation was defined as a p-value <0.05.

One-way ANOVA was used to test for a significant effect of the *rs2590498* (A/G) polymorphism of the gene coding for the human *OBPIIa* on participants' threshold olfactory scores, the number of active compounds smelled and the perceived intensity of each compound during the GC-O experiments, and the reported intensity of the coffee-odor pen.Post-hoc comparisons were conducted using Fisher's least significant difference (LSD) test. *P* values were adjusted by Bonferroni correction (adjusted P = P × number of groups being compared). Statistical analyses were performed using STATISTICA for WINDOWS (version 7.0; StatSoft Inc., Tulsa, OK, USA). P values <0.05 were considered significant.

A generalized linear model was used to determine the effect of age, sex and *OBPIIa* genotype on olfactory threshold score, the number of total-aroma and coffee-aroma compounds, the perceived intensity of total-aroma and coffee-aroma compounds, and the VARUs intensity of the coffee-odor pen.

Hardy-Weinberg equilibrium at the *OBPIIa* locus was assessed using the Hardy-Weinberg exact test (Genepop version 4.8.5; Testing: Hardy-Weinberg exact tests, op1), to determine whether the population behaves as a single randomly mating unit in the absence of intense viability selection at the sampled locus (Engels, 2009). Hardy-Weinberg expected frequency for each genotype of *OBPIIa* was also calculated for p2, 2pq, and q2 in the population by using the Levene correction (Genepop version 4.8.5; Estimating: Allele frequencies, various Fis and gene diversities, op5). This equation allows to correlate allele frequencies to genotype frequencies for the population.

3. Results

The mean values ± SE of the olfactory threshold score obtained by participants genotyped for the polymorphism of the gene encoding *OBPIIa* are shown in Fig. 1. Post-hoc analyses following a one-way ANOVA (F (2,78) = 12.23, $p < 0.001$; effect size 0.995) showed that participants who were homozygous for the A allele obtained significantly higher scores than those heterozygous ($p < 0.001$; Fisher's LSD test) or homozygous for the G allele ($p < 0.001$; Fisher's LSD test). No difference was found between heterozygous and homozygous GG individuals ($p = 0.39$; Fisher's LSD test).

Pearson's or Spearman's correlation analyses highlighted a positive relationship between the numbers of perceived total-aroma (Pearson $r = 0.58$; $p < 0.001$) or coffee-aroma compounds (Spearman $r = 0.47$; $p < 0.001$) vs. the olfactory threshold score (Fig. 2A and B). Furthermore, as shown in Fig. 2C and D, a positive relationship was also found between the olfactory threshold score and the average intensity with which the total-aroma (Spearman $r = 0.56$; $p < 0.001$) and coffee-aroma compounds (Pearson $r = 0.54$; $p < 0.001$), were perceived by each participant during the GC-O tests. The scatter plots in Fig. 2Ai-Di show the same correlations according to the AA or AG/GG *OBPIIa* genotype. Pearson's correlation analysis showed a significant relationship both between the olfactory threshold score and the number of perceived total-aroma (AA group: $r = 0.50$, $p = 0.01$; AG/GG: $r = 0.44$, $p < 0.001$) and coffee-aroma compounds (AA group: $r = 0.58$, $p = 0.002$; AG/GG: $r = 0.32$, $p = 0.017$), and between the olfactory threshold score and the average intensity with which the total-aroma (AA: $r = 0.45$, $p = 0.025$; AG/GG: $r = 0.37$, $p = 0.005$) and coffee-aroma compounds (AA: $r = 0.45$, $p = 0.024$; AG(GG: $r = 0.48$, $p < 0.001$) were perceived.

Fig. 3A and B show a significant effect of the *OBP* polymorphism on the number of both total-aroma (F (2,78) = 8.87; $p < 0.001$; effect size 0.967) and coffee-aroma compounds (F (2,78) = 6.06; $p < 0.005$; effect size 0.873) perceived by participants. In detail, post-hoc comparisons following one-way ANOVA showed that individuals carrying two A alleles perceived a significantly greater number of compounds than individuals carrying one G allele (Total-aroma: $p = 0.004$; Coffee-aroma: $p = 0.01$; Fisher's LSD test) or two G alleles (Total-aroma: $p < 0.001$; Coffee-aroma: $p = 0.002$; Fisher's LSD test). Statistical analyses indicate a significant effect of the *OBP* locus genotype also on the mean intensity with which compounds were perceived, both total-aroma (F (2,78) = 6.09; $p < 0.005$; effect size 0.875) and coffee-aroma (F (2,78) = 4.38; $p = 0.016$; effect size 0.741) (Fig. 3C, D). In fact, homozygous AA individuals perceived single molecules with a significantly higher intensity than that reported by both heterozygotes (Total-aroma: $p < 0.01$; Coffee-aroma: $p = 0.014$; Fisher's LSD test) and homozygous GG individuals (Total-aroma: $p < 0.005$; Coffee-aroma: $p = 0.012$; Fisher's LSD test). No difference was found between heterozygous and homozygous GG individuals, neither in the number of odor-active molecules nor in the intensity with which they were perceived ($p > 0.61$; Fisher's LSD test) (Fig. 3).

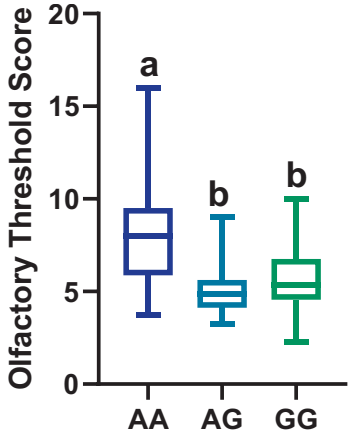

Fig. 1. Effect of the *OBP* genotype of participants on their olfactory sensitivity. Box-and-whisker plots showing the minimum, first quartile, median, third quartile, and maximum olfactory threshold score obtained by participants with genotype AA ($n = 25$), AG ($n = 16$) and GG ($n = 40$) of OBP. Different letters indicate a significant difference between genotypes ($p < 0.0001$; Fisher's LSD test subsequent to one-way ANOVA).

As shown in Fig. 4, Pearson's correlation test revealed a positive relationship between the perceived intensity of the coffee-odor pen and the olfactory threshold score of each participant ($r = 0.50$, $p < 0.001$), also according to their AA homozygous ($r = 0.53$, $p = 0.007$) or AG/GG hetero/homozygous genotype ($r = 0.33$, $p = 0.13$).

One-way ANOVA also revealed a significant effect of the *OBPIIa* locus genotype on the intensity value attributed to the coffee-odor pen (F (2,78) = 5.80; $p < 0.005$; effect size 0.858) (Fig. 5) and post-hoc tests showed that the intensity perceived by AA homozygous participants was significantly higher than that perceived by heterozygotes ($p < 0.005$; Fisher's LSD test) or GG homozygotes ($p = 0.005$; Fisher's LSD test). No difference was found between heterozygous and homozygous GG individuals ($p = 0.46$; Fisher's LSD test).

The effect of age, sex and *OBPIIa* genotype on olfactory threshold score, the number of total-aroma and coffee-aroma compounds, the perceived intensity of total-aroma and coffee-aroma compounds, the VARUs intensity of coffee-odor pen and their mutual relationship, analyzed by means of a generalized linear model, are shown in Table 1. In detail, based on the chi-square and p value, the analyses revealed that the *OBP* genotype represents the main effect for all variables considered. Furthermore, we found a significant mutual relationship between "age × *OBP* genotype" on the olfactory threshold score, and a significative effect of sex on the perceived intensity of total-aroma compounds, coffee-aroma compounds and coffee-odor pen.

Pearson's or Spearman's correlation tests were used to verify for a relationship not only between the number of compounds perceived, but also between the average intensity with which they were perceived during the GC-O tests, and the perceived intensity of the coffee-odor pen (Fig. 6). We found a relationship both with the number of active compounds (Total-aroma: Pearson $r = 0.67$, $p < 0.001$; Coffee-aroma: Spearman $r = 0.55$, $p < 0.001$), and with the average intensity with which the compounds were perceived (Total-aroma: Spearman $r = 0.58$, $p < 0.001$; Coffee-aroma: Pearson $r = 0.65$, $p < 0.001$).

Finally, Pearson's or Spearman's correlation analyses were used to test for a correlation between the hedonic valence attributed to the coffee-odor pen and to the total-aroma and coffee-aroma compounds (Fig. 7). We found a positive relationship between the hedonic valence attributed to the coffee-odor pen and the number of both total-aroma (Spearman $r = 0.49$; $p < 0.001$) and coffee-aroma (Spearman $r = 0.44$; $p < 0.001$) perceived as pleasant. Instead, a negative correlation was found between the number of total-aroma (Spearman $r = -0.41$; $p < 0.001$) and coffee-aroma (Spearman $r = -0.48$; $p < 0.001$) which are both defined as unpleasant by the participants and the hedonic valence for the coffee-odor pen.

The Hardy-Weinberg exact test showed a strong and highly significant deviation from Hardy-Weinberg equilibrium for the SNP *rs2590498* in the *OBPIIa* gene ($p < 0.001$), with a large heterozygote deficit (Fis ≈ 0.60) (Robertson & Hill, 1984; Weir & Cockerham, 1984) (Table 2). In addition, the Levene correction showed that the expected frequency for AA e GG genotypes in the population was lower than that observed. In contrast, the expected frequency of the heterozygous genotype was higher than the observed frequency. Specifically, for the AA genotype the expected frequency was 13.32 and the observed one was 25, for the heterozygous genotype the expected frequency was 39.35 and the observed one was 16, and for the GG genotype the expected frequency was 28.32 and the observed one was 40.

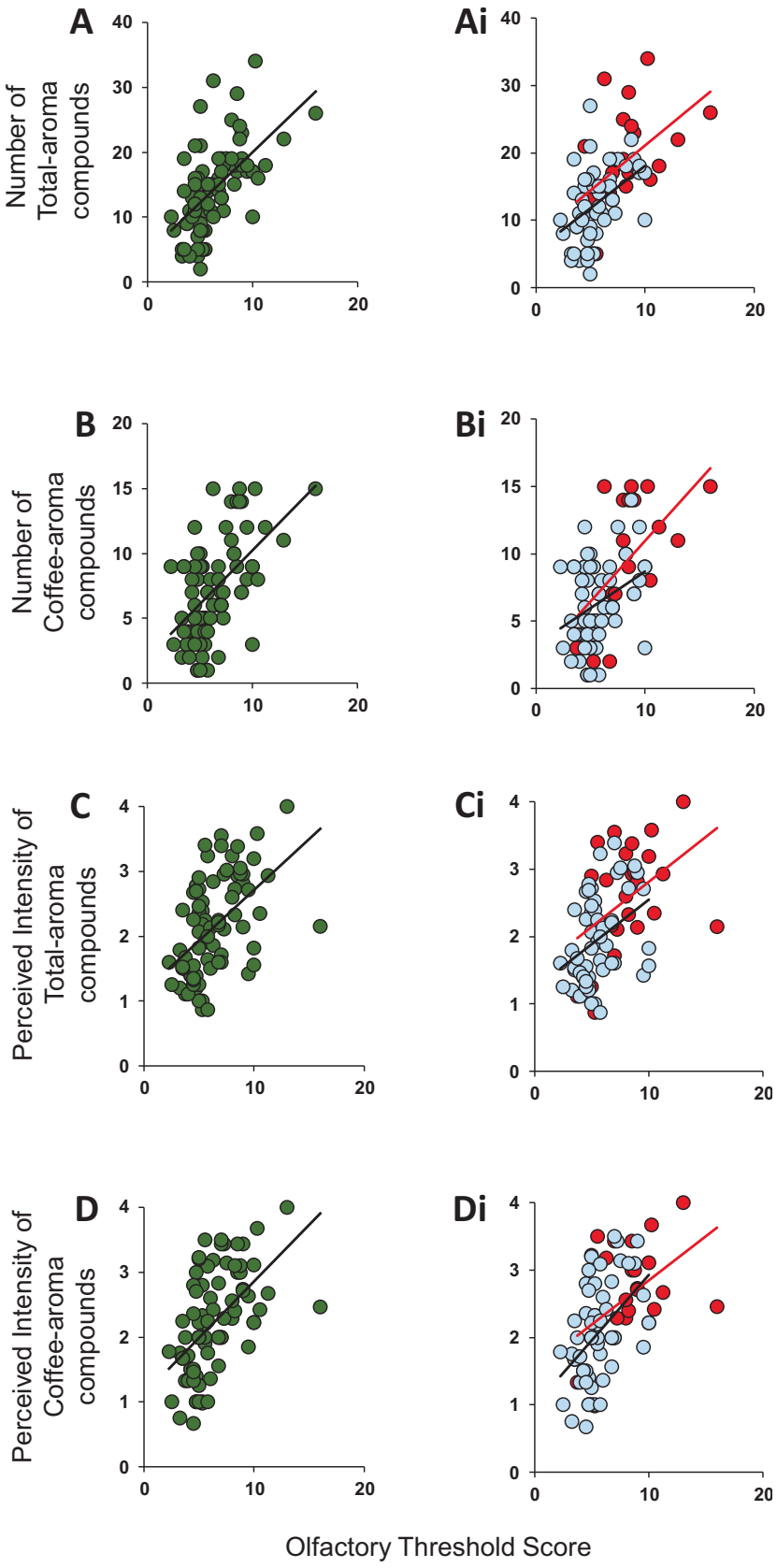

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Fig. 2. Relationship between olfactory sensitivity and ability to perceive single compounds. Scatter plots and correlation analyses between the olfactory threshold score and (A) the number of total-aroma compounds (Pearson $r = 0.58$, $p < 0.0001$), (B) the number of coffee-aroma compounds (Spearman $r = 0.47$, $p < 0.0001$) smelled by each participant, the average intensity with which (C) total-aroma compounds (Spearman $r = 0.56$, $p < 0.0001$) and (D) coffee-aroma compounds (Pearson $r = 0.54$, $p < 0.0001$) were perceived, also according to their AA (red dots) or AG/GG (light blue dots) *OBPIIa* genotype (Ai-Di). Pearson correlation between olfactory threshold score and (Ai) number of total-aroma compounds (AA: $r = 0.50$, $p = 0.01$; AG/GG: $r = 0.44$, $p < 0.001$), (Bi) number of coffee-aroma compounds (AA: r = 0.58, $p = 0.002$; AG/GG: $r = 0.32$, $p = 0.017$) smelled by each participant, the average intensity with which (Ci) total-aroma compounds (AA: $r = 0.45$, $p = 0.025$; AG/GG: $r = 0.37$, $p = 0.005$) and (Di) coffee-aroma compounds (AA: r = 0.45, $p = 0.024$; AG/GG: $r = 0.48$, p < 0.001) were perceived. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

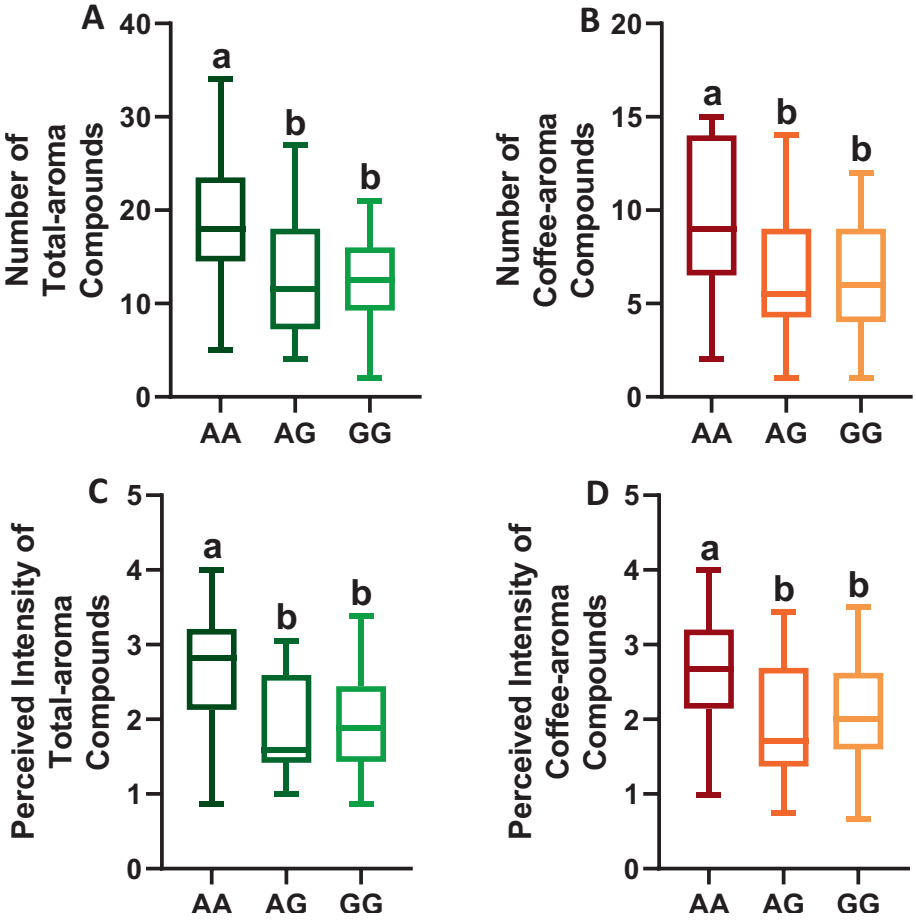

Fig. 3. Effect of the *OBP* genotype on the individual ability to perceive single compounds. Box-and-whisker plots showing the minimum, first quartile, median, third quartile, and maximum of the number of total-aroma compounds (A), the number of coffee-aroma (B) compounds, and the perceived intensity for total-aroma (C) and coffee-aroma (D) compounds smelled by participants during the Gas Chromatography-Olfactometry (GC-O) experiments, according to their *OBP* genotype. Different letters indicate significant differences between genotypes ($p < 0.02$; Fisher's LSD test subsequent to one-way ANOVA).

4. Discussion

The present research aimed to study the role of the *rs2590498* (A/G) polymorphism at the *OBPIIa* locus on the olfactory threshold performance of healthy individuals and on the different ability between individuals to perceive single molecules, both in quantitative and qualitative terms. In fact, it is known that due to environmental factors (Calderón-Garcidueñas et al., 2010; Sollai & Crnjar, 2023; Sorokowska et al., 2014), physiological factors (Min et al., 2021; Sorokowski et al., 2019), pathological factors (Sasaki et al., 2017; Walliczek-Dworschak et al., 2020; Wilson et al., 2009), and genetic factors (Melis et al., 2022; Melis et al., 2024; Silva Teixeira et al., 2016), the olfactory function of individuals can vary from normosmia (normal function), to hyposmia (reduced or compromised function) or anosmia (totally or specifically absent function), both to complex stimuli and single compounds (Jafek et al., 1990; O'Connell et al., 1989; Sollai et al., 2020). Among genetic factors, an important role appears to be played by the allelic variability of the gene encoding *OBP*, which is present in the human olfactory mucosa and is important for facilitating the binding of odorants to olfactory receptors. Recent studies have shown that individuals with the AA genotype have a lower olfactory threshold than individuals carrying at least one minor G allele (Sollai et al., 2019).

Our results show a significant effect of the *OBP* polymorphism on the olfactory threshold score. Specifically, we found that individuals with the AA genotype achieved a significantly higher score than heterozygous or GG homozygous individuals, thus indicating a lower olfactory perception threshold. We subsequently assessed whether individuals with a higher olfactory threshold also had a greater ability to perceive odor-active compounds. Correlation analyses showed a positive relationship between the olfactory threshold score and both the number of aroma-active compounds smelled by each individual and the average intensity with which them was perceived. Specifically, our data show that individuals with lower olfactory thresholds can perceive a greater number of compounds and also with higher intensity, both in terms of total-aroma and coffee-aroma compounds, compared to those with higher olfactory thresholds (as indicated by the lower scores obtained).

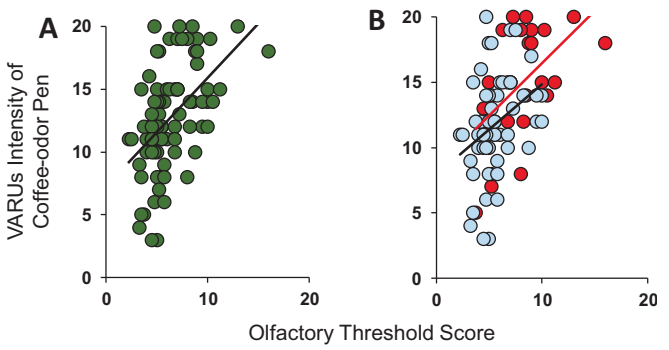

Fig. 4. Relationship between perceived intensity for coffee-odor pen and olfactory sensitivity. Pearson's correlation analyses between the intensity perceived by each participant for the coffee-odor pen and (A) his/her olfactory threshold score (r = 0.50, p < 0.0001), also (B) according to their AA (red dots; $r = 0.53$, $p = 0.007$) or AG/GG (light blue dots; $r = 0.33$, $p = 0.13$) genotype. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

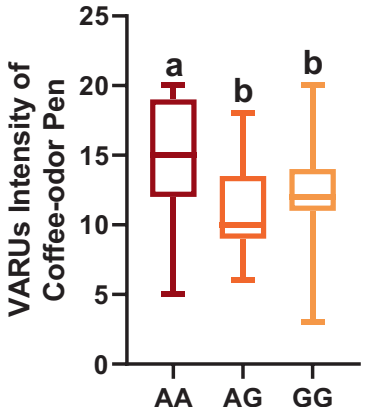

Fig. 5. Effect of the *OBP* genotype on the perceived intensity for the coffee-odor pen. Box-and-whisker plots showing the minimum, first quartile, median, third quartile, and maximum of perceived intensity evoked by the coffee-odor pen in participants with genotype AA ($n = 25$), AG ($n = 16$) and GG ($n = 40$) of OBP. Different letters indicate a significant difference between genotypes ($p < 0.02$; Fisher's LSD test subsequent to one-way ANOVA).

Once this relationship was established, we evaluated whether the number and intensity with which odor-active compounds are perceived were also determined by the *OBP* polymorphism. Again, we found that both the number of total-aroma and coffee-aroma compounds, as well as the intensity with which each of them was perceived, was greater for individuals homozygous for the A allele: these results are consistent with previous studies that have shown that the A allele is associated with a higher olfactory sensitivity both orthonasal and retronasal (Sollai et al., 2019; Tomassini Barbarossa et al., 2017); meanwhile, the minor G allele can decrease the expression of OBP protein and, consequently, the olfactory performance of individuals (Melis et al., 2019). These present and previously reported results are consistent with the idea that olfactory perception of both simple and complex odors can be considered, at least in part, as the phenotypic manifestation resulting from the allelic diversity of the *OBP* gene.

An interesting aspect that we analyzed was whether there is a relationship between the perception of the blend and that of the single compounds, and whether this is somehow linked to the individual's olfactory threshold. Although an analysis of a single coffee aroma would limit a generalization of the result, our data suggests a direct relationship between the number and intensity with which single compounds are perceived and the intensity reported for the coffee blend.

Table 1
Generalized linear model analyses. Effect of *OBPIIa* genotype, age and sex, and their mutual relationship, on olfactory threshold score, number of total-aroma and coffee-aroma compounds, perceived intensity of total-aroma and coffee-aroma compounds, Visual Analogue Rating Units (VARUs) intensity of coffee-odor pen.

Variable	Factor	X^2	P-value
Olfactory threshold score	Sex	0.79	0.78
	Age	0.79	0.78
	OBP genotype	22.67	< 0.0001
	Sex × *OBP* genotype	8.35	0.015
Number of Total-aroma compounds	Sex	0.75	0.39
	Age	0.92	0.09
	OBP genotype	19.06	< 0.0001
	Sex × *OBP* genotype	3.63	0.16
Number of Coffee-aroma compounds	Sex	0.32	0.57
	Age	2.52	0.11
	OBP genotype	13.94	< 0.001
	Sex × *OBP* genotype	3.85	0.15
Perceived Intensity of Total-aroma compounds	Sex	3.61	0.06
	Age	11.55	< 0.001
	OBP genotype	15.56	< 0.001
	Sex × *OBP* genotype	0.37	0.83
Perceived Intensity of Coffee-aroma compounds	Sex	1.74	0.18
	Age	9.92	< 0.005
	OBP genotype	11.41	< 0.005
	Sex × *OBP* genotype	0.21	0.90
VARUs Intensity of Coffee-odor Pen	Sex	0.12	0.91
	Age	6.39	0.012
	OBP genotype	13.37	< 0.005
	Sex × *OBP* genotype	0.73	0.69

Furthermore, our data revealed that the olfactory threshold score obtained by each individual is significantly correlated with the intensity with which the complex coffee odor is perceived. Finally, our results showed that the number of compounds perceived and their perceived intensity are linked to the *OBP* polymorphism. Individuals carrying two A alleles perceive a greater number of compounds belonging to the blend and also with greater intensity than heterozygous or homozygous GG individuals. Overall, our results provide an explanation for the underlying causes of the variability with which individuals perceive the complex aroma of coffee. On the one hand, a low olfactory threshold favors the perception of the individual compounds that compose the complex aroma of coffee, both in terms of number and intensity with which they are perceived. On the other hand, a greater number of odor-active compounds smelled and a higher intensity of perception for each of them lead to a higher intensity of perception for the complex blend. These considerations are very important if we consider that not all compounds within the blend have the same sensorial importance: in fact, it has been previously shown that the number of perceived compounds is directly related to the intensity reported for the blend and that the most sensorially active molecules, i.e. those perceived by the greatest number of participants, are those that contribute most to the aroma of the blend (Blank et al., 2001; Brattoli et al., 2013; Ferreira, 2012a, 2012b; Iannario et al., 2012; Jordán et al., 2001; Schilling et al., 2010; Sollai et al., 2020). This means that the number of compounds perceived determines the intensity with which each of us perceives a

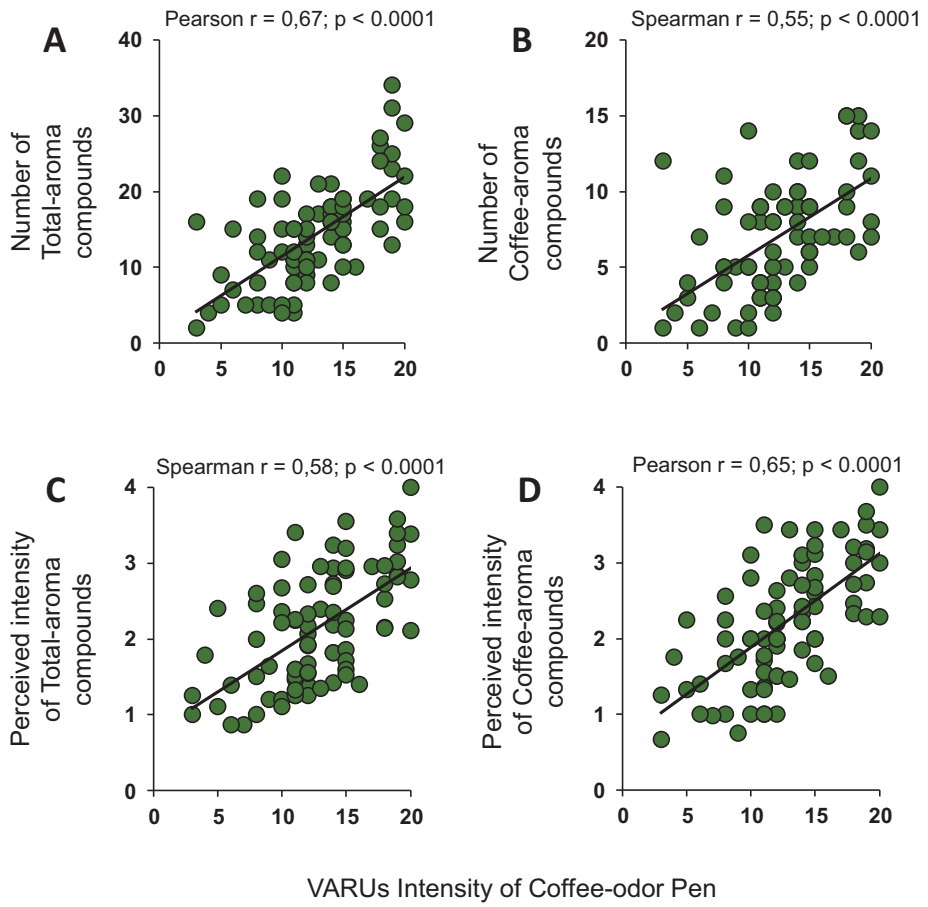

Fig. 6. Relationship between perceived intensity for coffee-odor pen and olfactory sensitivity. Correlation analysis between the intensity perceived for coffee-odor pen by each participant and the number of total-aroma (A) and coffee-aroma compounds (B) smelled, and the perceived average intensity for total-aroma (C) and coffee-aroma compounds (D).

complex odor. This is very important because if the intensity with which a food is perceived is low, sensorial satiety will be reached later and this, as is known, influences the beginning, duration and end of a meal (Bolhuis et al., 2012; Gaillet-Torrent et al., 2014; Power & Schulkin, 2008; Ramaekers et al., 2014; Velluzzi et al., 2022; Yin et al., 2017).

During the GC-O experiments, participants were also able to express a personal evaluation of the hedonic valence attributed to the perceived odor. Specifically, they were asked to report whether the odor was pleasant or unpleasant. Therefore, as a final objective, we assessed whether the reported pleasantness/unpleasantness of the coffee-odor pen was related to the number of odor-active compounds defined as pleasant or unpleasant. Our results show that there is a positive correlation between the number of pleasant compounds and the perceived pleasantness for the coffee-odor pen. Conversely, a negative correlation was found between the pleasantness for the coffee-odor pen and the number of compounds defined as unpleasant. These findings are consistent with a previous study, which found that the reported pleasantness of the complex banana odor was directly related to that of the odor of isoamyl acetate, which is used in the food industry to impart a banana flavor to foods and beverages and has been identified as the most sensorially active within the blend (Sollai et al., 2020). This is very important because it provides a possible explanation for why the same complex odor is perceived as pleasant by some individuals and unpleasant by others. Just as intensity is related to the number of odor-active molecules, pleasantness is related to how odor-active compounds are perceived. Therefore, an individual who perceives the pleasant odor of coffee, perceives most of the odor-active compounds as pleasant. Conversely, those who perceive the unpleasant odor of coffee perceive the sensorially active molecules within the blend as unpleasant.

Since sensory properties have been reported in the literature to be among the factors that contribute to making an individual a coffee drinker or non-drinker, these aspects are of particular importance (Samoggia et al., 2020).

Although the considerations discussed are largely supported by the results of this study, some limitations deserve consideration. First, we used only one coffee blend. However, we are confident that the results will be generalizable and useful for the coffee industry, since the goal was not to identify which compounds are sensorially active, but rather how their perception varies across individuals, and which factors, in this study the role of *OBPIIa* genotype, may contribute to the observed inter-individual variability. These results aim to provide the coffee industry with information on the fact that perception is highly variable and that several factors can influence it. Therefore, they suggest to the coffee industry that the consumer's sensory characteristics are particularly important in developing palatable blends. Furthermore, although each blend presents specific characteristics, a comparison with other blends studied showed that the volatile compound profile found in this study is largely similar to those reported in the literature (Akiyama et al., 2003; Caporaso et al., 2018; Gloess et al., 2018; Lee et al., 2017; López-Galilea et al., 2006; Majcher et al., 2013; W. Sunarharum et al., 2014a; Yang et al., 2016; Zapata et al., 2018). It should also be noted that dynamic headspace sampling is considered the most suitable method for obtaining an extract whose volatile composition is closely related to the aroma quality attributed by the consumer (van Den Dool & Kratz, 1963). Furthermore, the dynamic headspace sampling method has the advantage of obtaining extracts for GC–MS and sensory evaluation via GC-O analysis by a human evaluator (Nuzzi et al., 2008).

Second, the Hardy–Weinberg equilibrium (HWE) test revealed a

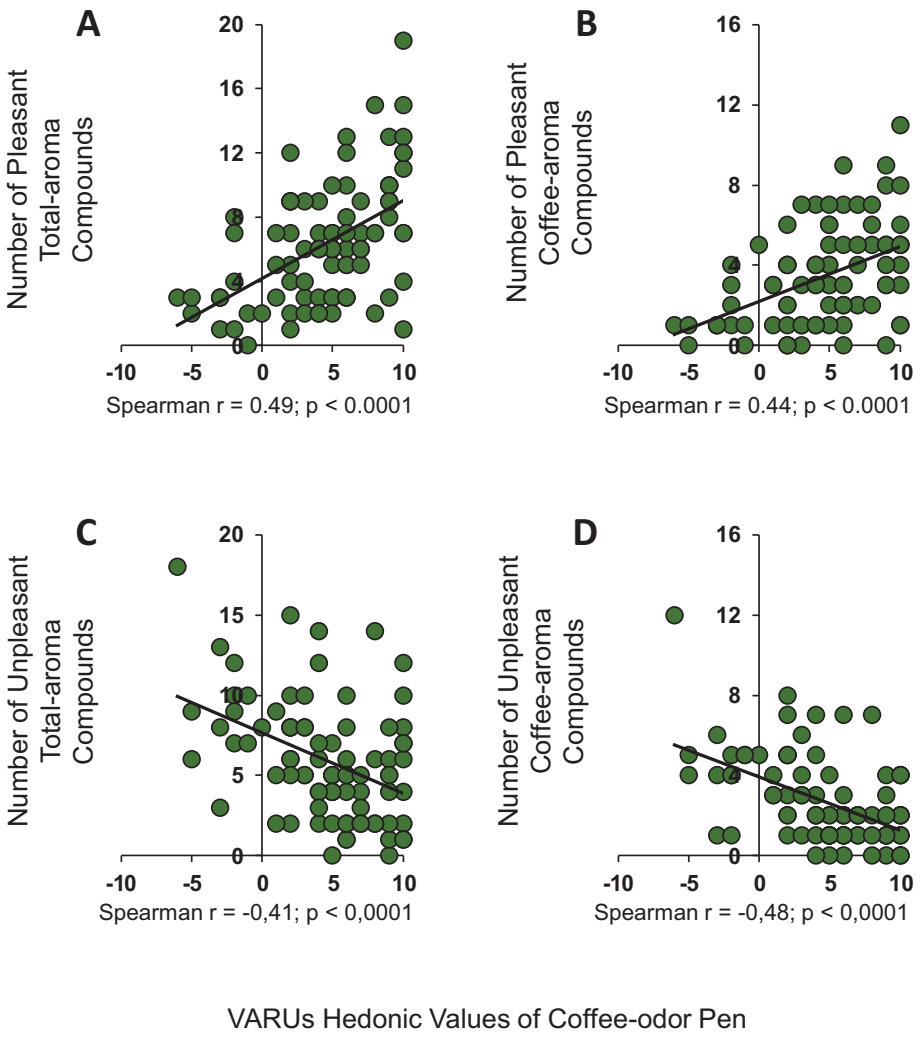

Fig. 7. Relationship between single molecules hedonic valence and that for the coffee-odor pen. Correlation analysis between the reported hedonic valence for the coffee-odor pen and the number of total-aroma (A) and of coffee-aroma compounds (B) perceived as pleasant, and the number of total-aroma (C) and coffee-aroma compounds (D) perceived as unpleasant by each participant.

Table 2
Hardy-Weinberg equilibrium analyses. Hardy-Weinberg equilibrium results for the SNP *rs2590498* in the *OBPIIa* gene.

		Observed n (%)	Expected n (%)	*P*-value[a]
rs2590498				
	Genotype			
	AA	25 (30.8)	13.3 (16.4)	< 0.001
	AG	16 (19.8)	39.4 (48.6)	
	GG	40 (49.4)	28.3 (35.0)	

[a] *P*-value relative to the Hardy-Weinberg equilibrium for the population derived from the Hardy-Weinberg exact test ($n = 81$). The expected frequency for each genotype was calculated by using Levene's correction.

highly significant deviation for *rs2590498* in the *OBPIIa* gene, characterized by a marked deficit of heterozygotes and an excess of homozygotes, which may reflect specific demographic and genetic features of the studied population. Specifically, the present study was conducted in a genetically homogeneous cohort residing in Sardinia, an island population widely considered genetically isolated due to its long-term geographic isolation, genetic drift and relatively limited gene flow with mainland populations (Caló et al., 2010; Cavalli-Sforza et al., 1995; Chiang et al., 2018; Francalacci et al., 2003). Previous genomic studies have shown that Sardinians exhibit distinctive genetic characteristics compared with other European populations, including increased homozygosity and higher inbreeding coefficients than mainland Italians, consistent with the island's complex demographic history (Di Gaetano et al., 2014). Such population characteristics may contribute to deviations from Hardy–Weinberg expectations, particularly in relatively small cohorts. Therefore, the pattern observed for *rs2590498* may reflect the specific genetic background of the Sardinian population. However, despite this uneven distribution, the observed effects remained statistically significant, and the analyses showed a high statistical power, supporting the robustness of the main findings. Nevertheless, future studies with larger and more balanced samples would be useful to further confirm these observations.

5. Conclusions

In conclusion, each individual's perception of a complex odor is different and subjective. Quantitatively, it appears to depend both on the number of sensorially active molecules in the blend and the average intensity with which these molecules are perceived. Qualitatively, it appears to be determined by the hedonic valence attributed to each molecule in terms of pleasantness/unpleasantness. Furthermore, these factors appear to be closely related to the olfactory function threshold and the *rs2590498* (A/G) polymorphism of the *OBPIIa* locus.

Studying the factors underlying inter-individual differences and the

organoleptic properties of the coffee blends, which influence not only perceived pleasantness, but also intensity, can be of great interest for both the industry and coffee consumers in understanding why an individual is a coffee consumer or not. For the coffee industry, individual differences are important because knowing that a blend composed of certain molecules can be more or less intense and pleasant allows for a more precise choice of beverage pairing. For coffee consumers, this information can be useful in choosing the right blend. We believe that, by understanding the key molecules that influence the olfactory perception of coffee aroma, and how these vary based on the individual olfactory function, the coffee industry could market blends diversified by sex and olfactory performance.

CRediT authorship contribution statement

Daniela Diana: Writing – review & editing, Methodology, Investigation, Formal analysis. **Melania Melis:** Writing – review & editing, Methodology, Investigation. **Paolo Solari:** Writing – review & editing, Investigation. **Iole Tomassini Barbarossa:** Writing – review & editing, Resources. **Roberto Crnjar:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Giorgia Sollai:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the UNIVERSITY HOSPITAL OF CAGLIARI (Prot. PG/2021/14278 del 22.09.2021).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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