On the relationship between olfactory sensitivity and personality in HIV-seropositive and healthy men

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Published online: 12 March 2018

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Abstract

The aim of this study was to further elucidate the relationship between the olfactory system and psychosocial functioning. Previous studies have shown that olfactory sensitivity is related to traits such as extraversion, agreeableness, and emotionality. In this study, the model of agency and communion as well as additional measures of social activity were used. The possible influence of HIV infection, believed to affect both chemosensory functions and social behaviors, was examined. 103 male participants were analyzed, of whom 45 were infected with HIV. Olfactory sensitivity was significantly related to the level of communion ($p = .01$), trait defined as interpersonal warmth, devotion to others, and morality. The effect was independent of the presence of HIV. Eagerness to engage in social activities, a construct indicating how actively one takes part in social life, was positively associated with olfactory sensitivity only in HIV+ individuals ($p = .003$). This result may imply that active participation in social life can buffer olfactory impairments in HIV patients.

Keywords Agency and communion · HIV · Sensory filter · Social activity · Social support

Introduction

People's behaviors are inseparable from the way in which they perceive the world. It has recently become clear that not only visual and auditory stimuli, but also olfactory cues have a strong impact on how we interact with the world (Stevenson

2010). Olfaction helps us avoid environmental hazards and perceive social information, just as it helped our evolutionary progenitors to survive and pass on their genes.

There is a rich body of evidence documenting how humans use chemosensory cues alone to infer information about others. For instance, it has been demonstrated that people tend to accurately identify the sex (Russell 1976; Schleidt 1980), age group (Mitro et al. 2012), and even health status (Olsson et al. 2014) of those they smell. Previous studies have also shown that even more specific information can be inferred – people appear to be able to accurately identify the body odors of their children, siblings (Porter and Moore 1981), and even friends (Olsson et al. 2006). Recently, it has been reported that other individuals' personality traits can be estimated above chance level based solely on their body odors (Sorokowska et al. 2012). The correlations between donors' personality traits self-assessment and the independent judgements made by 20 raters based on odors alone were strongest for extraversion (.36), neuroticism (.34) and dominance (.29) – traits related to social functioning.

Information about demographic characteristics or general personality traits isn't all that can be extracted from body odors. Sociochemosensory cues also contain information about

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donors' current emotional states (de Groot et al. 2012). The emotional valence of such stimuli was reported to affect the recipient's own emotional state. For instance, in a study conducted by Prehn et al. (2006), participants exposed to the odor of scared people demonstrated an enhanced startle blink amplitude in comparison to subjects exposed to a neutral odor. Moreover, in a study by Chen et al. (2006), female participants exposed to the body odor of scared donors performed a word-association task more accurately than and as quickly as participants exposed to an emotionally neutral body odor and those in the control group. However, when the pair of words contained ambiguous information, their reaction time dropped. These results suggest that chemosensory fear signals are treated as a warning of possible danger. Having received such a signal, individuals become warier and use their cognitive capabilities more efficiently. Apparently, the odors of aggressive people play a similar warning role. People exposed to odors of potentially dangerous individuals - males participating in a boxing session - also react with anxiety (Mitic et al. 2015).

Taking into account both the aforementioned role of human olfaction in everyday functioning and inter-individual variation in levels of olfactory skills, it is natural to ask whether olfactory abilities and stable personality traits are associated in any way. Recently, Croy et al. (2011) proposed an interesting model to explain how environmental stimuli, including odors, stimulate the development of personality characteristics depending on the capacity of the sensory system. According to their hypothesis, sensory thresholds work as filters modulating the amount of received stimuli and the influence they have on personality development. As such, individuals with more sensitive olfaction receive and process greater amounts of chemosensory input, including input of social relevance. In turn, they are able to appraise other peoples' personalities and emotional states more accurately and be more considerate of their needs. Croy et al. assessed personality traits as described in the five-factor model developed by McCrae and Costa (2003). According to this theory, there are five dimensions of human personality: extraversion, neuroticism, openness to experience, agreeableness, and conscientiousness. It appeared that sensitivity to the smell of n-butanol was positively related to agreeableness ($r = .27, p < .05$), the trait related to interpersonal skills, interest in social life, and concern about other people. This result is consistent with the sensory filter hypothesis and previous knowledge about the role of human olfaction in social cognition (Stevenson 2010).

Results of other studies also indicate that olfaction appears to be associated with social traits. For example, it has been reported that the aggregated level of sensitivity to different odors, such as amyl acetate, exaltolide, muscone, butanol, dupical, and musk, is positively correlated with extraversion (Koelega 1970). On the other hand, Pause et al. (1998) reported that olfactory sensitivity was not significantly correlated with extraversion, but rather with neuroticism. Similarly, Herberner

et al. (1989) reported that extremely shy male adults have better olfactory sensitivity than sociable ones. Havlíček et al. (2012) found that of the five-factor personality model dimensions, only neuroticism (in particular, anxiety and self-consciousness subscales) was significantly (positively) correlated with the outcomes of olfactory sensitivity tasks. Recently, Mahmut and Stevenson (2016) reported that olfactory sensitivity and identification are negatively correlated with psychopathy and positively correlated with empathy.

Collectively, these results suggest that olfactory sensitivity is associated with traits related to social and emotional functioning. Individuals with more sensitive olfactory systems were found to be, on one hand, more sociable, empathic, out-going, agreeable and, on the other hand, more emotional, self-conscious, and anxious. Such a personality pattern might develop, in line with the model of Croy et al. (2011), as an effect of the reception of rich olfactory input, possibly containing information relevant to social cognition. As such, individuals with sensitive olfaction receive more sociochemosensory stimuli, which allows them to unconsciously infer accurate information about people they interact with. This, in turn, helps them feel more comfortable during social interactions and enhances the development of traits such as extraversion and agreeableness. However, sociochemosensory stimuli also contain information about the emotional states, which affect the recipient's own mood. In particular, the ability to infer information about states of anxiety or anger in others from their body odors may lead to a tendency to react with anxiety, increasing levels of neuroticism in those with more sensitive olfaction.

The studies discussed above focus on the general population. It is of interest, however, whether the relationship between olfactory sensitivity and personality also applies to individuals whose levels of chemosensory skills and socioemotional functioning have both been affected by a clinical condition. This paper examines the association between olfaction and personality in men infected with Human Immunodeficiency Virus (HIV).

There is a significant body of evidence documenting chemosensory impairment in HIV-seropositive individuals. The increased odor detection threshold is even suspected to be one of the earliest symptoms of infection (Mueller et al. 2002). While olfactory skills strongly dependent on cognitive functions, such as odor identification, decrease as the infection progresses (Westervelt et al. 1997), olfactory sensitivity declines in the early stages of infection and then remains constant (Zucco and Ingegneri 2004).

HIV infection also affects social functioning, as it is still associated with a stigma which has not lessened despite increasing public awareness and advances in treatment (Herek et al. 2002). Hence, many HIV-seropositive individuals isolate themselves and are reluctant to inform their family and friends about their infection (Leask et al. 1997). However, the

disclosure of infection to others increases the number of possible sources of satisfying social support, which is one of the strongest determinants of life quality for HIV+ individuals (Friedland et al. 1996; Swindells et al. 1999).

The aim of this study was to investigate whether the relationship between olfactory sensitivity and personality in HIV+ men differs from the general population. Socially relevant traits are of special interest here, because - as discussed above - they appear to have been functionally connected to olfaction since our evolutionary past. We hypothesized that the impairment of olfactory functions is milder in those HIV-infected individuals who are social and caring by nature. It was also suspected that the level of olfactory performance is associated with satisfaction with received social support. It would suggest that some personality characteristics can buffer the effect HIV has on the olfactory system.

A secondary goal of this study was to investigate how olfactory sensitivity is related to traits of personality theory other than the five-factor model. The model of general motivational orientations, namely: agency and communion (Bakan 1966; Helgeson 1994) was used. Agency indicates striving for achievement, competitiveness, and independence. This construct correlates with extraversion, conscientiousness (Ward et al. 2006), self-esteem, lower anxiety and lower depression (Sharpe and Heppner 1991). Communion, on the other hand, indicates warmth, devotion to others, and morality. It correlates with empathy (Davis 1983), neuroticism and agreeableness (Ward et al. 2006), social self-esteem (Hawkins et al. 1983) and the amount of help asked for during stress events (Butler et al. 1985). In line with the sensory filter model, we suspected that communion, as an orientation toward others, would be positively correlated with olfactory sensitivity.

Materials and Methods

Selection of Participants

The data used in this analysis were gathered in a larger research project on cognitive and chemosensory functioning in HIV infection. The study was approved by Ethics Committee of the University of Warsaw and it is compatible with the Declaration of Helsinki. HIV+ participants were recruited from male patients of Warsaw's Hospital for Infectious Diseases, who were infected via sex and had been receiving HAART (highly active antiretroviral therapy) treatment for a minimum of 10 months. The HIV- group was recruited from the general population to match the features of the clinical group. The general exclusion criteria included a history of chronic or progressive neurological disorders, current psychosis, history of learning disability or attention deficit disorder, laryngological disorders, illicit drug use within the last five years. Because the major project included fMRI,

claustrophobia served as an additional exclusion criterion. The participants gave written informed consent.

The analysis was performed on a subgroup of 103 males out of 200 recruited, whose olfactory functioning, based on otolaryngologic examination, wasn't affected by laryngological factors and whose psychological self-assessment questionnaires were not missing any data. Age of the selected participants ranged from 24 to 75 years. The analyzed subgroup included 45 HIV+ individuals and 58 HIV- participants. Table 1 shows demographic and medical characteristic data for the studied sample. The groups didn't differ in mean age, number of years of education, or level of cognitive functioning, as assessed by the Mini Mental State Examination (Polish adaptation - Stańczak 2010).

Olfactory Sensitivity Assessment

The assessment of sensitivity was part of a chemosensory examination carried out in the Institute of Psychiatry and Neurology in Warsaw. Sniffin' Sticks (Burghardt, Wedel, Germany), a commercially available test, was used. It is one of the most popular and psychometrically sound standard tests used in olfactory assessment (Hummel et al. 2007). Following the standard procedure, olfactory sensitivity was examined in trials consisting of a randomized presentation of three pens, one containing a particular concentration of n-butanol as the odorant, and two others containing the odorless solvent. The forced choice procedure was applied, where blindfolded participants had to indicate the stick with the odorant. The triplets were first presented starting with the lowest concentration. If the participant was unable to correctly identify a target pen, another triplet was presented with the target pen containing a higher concentration of the target substance. When the participant correctly identified the target pen twice in row, the order of presentation was reversed and the participant was once again presented with a triplet with the target pen containing a lower concentration. A final score, ranging from 1 to 16, reflected the mean of the last four staircase reversals, with a higher score reflecting a lower olfactory threshold, what indicates more sensitive olfaction.

Personality Assessment

Agency/Communion In the Assessment of personality orientations, an unpublished Polish translation of the Personal Attribute Questionnaire (PAQ) (Helmreich et al. 1981) was used. The inventory contains 24 items, each consisting of a pair of attributes with opposite meaning, reflecting opposite poles of a continuum. Participants indicate, on a scale ranging from 0 to 4, where on the continuum they are. The inventory consists of three independent subscales: Masculinity, Femininity, and Masculinity-Femininity. The first two are commonly used to assess agency and communion respectively (Abele 2003; Helgeson 1994). The attributes of the agency (Masculinity)

Table 1 Mean values (with standard deviations) of participants' demographic and medical characteristics and *p*-values for *t*-tests comparing the means of HIV+ and HIV- groups

Demographic characteristics of participants				
	All participants <i>n</i> = 103	HIV+ participants <i>n</i> = 45	HIV- participants <i>n</i> = 58	<i>p</i> -values
Age	42.16 (12.06)	39.68 (10.76)	44.08 (12.74)	.09
Eduyears	16.42 (2.91)	16.00 (2.94)	16.75 (2.88)	.18
MMSE score	29.25 (1.10)	29.24 (1.07)	29.26 (1.13)	.91
Smokers/nonsmokers	28/75	13/32	15/43	
MSM/heterosexual	83/20	43/2	40/18	
Medical characteristics of HIV+ participants				
Years since HIV detection	6.64 (6.31)			
CD4 lowest value	277.02 (137.14)			
Viral load highest value	190,261.22 (504,033.80)			
Years since cART	5.18 (5.28)			

scale indicate competitiveness, self-confidence, and instrumentality (Sample pairs of attributes: “Not at all independent – Very independent”, “Very passive – Very active”). On the other hand, the attributes of the communion (Femininity) scale indicate expressivity, warmth, and kindness (sample pairs of attributes: “Not at all able to devote self completely to others – Able to devote self completely to others”, “Not at all helpful to others – Very helpful to others”). It is important to note that despite the scales' traditional names, the attributes included in them are desirable for individuals of both sexes. The reliability of the Polish versions of the scales measured with Cronbach's alpha is satisfactory ($\alpha = .76$ for the agency scale, and $\alpha = .80$ for the communion scale).

Social Activity To determine how eager individuals are to engage in social activities, the Social Activity Questionnaire (SAQ), developed for use in this project was used. It consists of six items which assess how eagerly individuals engage in different kinds of social interactions: (1) How willingly have you offered assistance to others in case they needed it? (2) How willingly have you supported others by showing them respect, approval or acceptance when they need it? (3) How willingly have you helped others if they could not fulfill their duties? (4) How willingly have you listened to others trying to understand and empathize, when they needed it? (5) How willingly have you supported others by comforting them or showing them compassion in hard moments? (6) How willingly have you offered advice to others in case they could not find a solution to a problem? The items are rated on 4-point scale, ranging from 1 – Very unwillingly, to 4 – Very willingly. Scores range from 4 to 24, with higher scores indicating greater prosocial orientation, compassion, and readiness to actively support others. The internal consistency of this questionnaire on the analyzed group is acceptable ($\alpha = .89$).

Satisfaction with Social Support Satisfaction with received social support was assessed with the Satisfaction subscale of an unpublished Polish version of the 6-item short form of the Social Support Questionnaire (Sarason et al. 1987), translated for the use in this project. Items describing different forms of support are rated on a 6-point scale (1 – Very dissatisfied, 6 – Very satisfied). Scores varied from 6 to 36, and reflect the degree to which an individual's satisfaction with received social support is adequate to their needs. The internal consistency of the Polish version of the scale is high ($\alpha = .89$).

Data Analysis

The IBM SPSS 22 statistical package was used. Descriptive statistics for the olfactory test and self-assessment measures are presented in Table 2. Because the assumption of normality of distributions for many variables was violated, the means of these variables for HIV+ and HIV- participants were compared with Mann-Whitney U test. Before the main hypotheses were tested, the multiple linear regression analysis was performed to examine if sexual orientation of participants influence the olfactory performance. The general relationship

Table 2 Means and standard deviations of olfactory and psychosocial variables and *p*-values for Mann-Whitney test comparing the means of HIV+ and HIV- groups

	HIV+ participants <i>n</i> = 45	HIV- participants <i>n</i> = 58	<i>p</i> -value
Olfactory sensitivity	8.14 (2.64)	7.34 (2.20)	.13
Agency	20.78 (5.43)	19.10 (4.66)	.13
Communion	22.24 (5.42)	21.6 (4.75)	.34
Social activity	20.29 (2.84)	19.45 (3.36)	.24
Satisfaction with social support	31.36 (4.90)	30.36 (4.82)	.17

between olfactory sensitivity and psychological characteristics for all participants was examined by performing a zero-order correlational analysis. Then, a series of moderation analyses were performed to examine if these relations are modified by HIV infection. The moderation analyses were done using the PROCESS macro (Hayes 2013). The bootstrapped (5000 resamples) 95% confidence intervals for the specific indirect effects were estimated.

Results

Mean scores of olfactory sensitivity, agency and communion, social activity, and satisfaction with social support were compared between HIV+ and HIV- groups. The results are presented in Table 2. The groups didn't differ significantly in olfactory sensitivity or in any of the psychosocial measures.

Because HIV- group included greater proportion of heterosexual participants to MSM (men who have sex with men) than HIV+ group (as presented in Table 1), the linear regression analysis was performed to examine if sexual orientation had an influence on olfactory sensitivity. Since heterosexual participants were significantly older than MSM (mean age of heterosexual participants: 53.85(11.75); mean age of MSM participants: 39.34(10.37), $U = 296.5$; $p < .001$), age was another variable included in the regression model. The regression equation was significant, $F(2,100) = 10.48$; $p < .001$. Age was a significant predictor of olfactory sensitivity ($\beta = -.38$; $p < .001$). Sexual orientation, however, didn't predict the dependent variable significantly ($\beta = -.07$; $p = .48$).

To examine if olfactory sensitivity is related to personality and social functioning, correlation analysis was performed. The results are presented in Table 3. Because communion and eagerness to engage in social activity both relate to similar personality patterns, Bonferroni correction was applied for correlations of these constructs with olfactory sensitivity to reduce the chance of committing Type I error (α value lowered to .025). Performance on the odor detection task was positively related to level of communion and eagerness to engage in social activities. As expected, no relationship between olfactory sensitivity and agency was found. The correlation between olfactory sensitivity and satisfaction with

social support was also not significant. The scatterplots for correlations are presented on Figs. 1, 2, 3 and 4.

To examine if observed relations differed depending on HIV status, a series of moderation analyses were conducted. Olfactory sensitivity was regressed, in turn, on communion, eagerness to engage in social activity, and socialization index with dichotomic HIV status variable as moderator.

The model with communion as independent variable was significant ($F(3,99) = 3.22$; $p = .03$). The level of communion significantly predicted olfactory sensitivity ($\beta = .10$, $p = .01$). This effect wasn't modified by HIV status ($\beta = .02$; $p = .66$). Also, the simple effect of HIV status wasn't significant ($\beta = .37$; $p = .14$). It appears that the more other-oriented and caring an individual is, the more sensitive olfaction they have, independent of their HIV status.

However, there was a significant interaction between HIV status and level of eagerness to engage in social activities. The model was significant ($F(3,99) = 4.07$; $p = .01$). Both the SAQ score ($\beta = .21$; $p = .01$) and interaction effect between SAQ score and HIV status ($\beta = .18$; $p = 0.04$) on olfactory sensitivity were significant. The simple effect of the moderator wasn't significant ($\beta = .29$; $p = .23$). Conditional effects analysis revealed that the relationship between eagerness to engage in social activity and olfactory sensitivity was significant only in the HIV+ group ($\beta = .42$; $p = .003$). For HIV- participants, this effect was not significant ($\beta = .05$; $p = .60$). Thus, it appears that while declared level of engagement in social activities is, in fact, positively associated with olfactory sensitivity, this is only the case among HIV patients.

Models with satisfaction with social support ($F(3,99) = 1.57$; $p = .20$) and with agency ($F(3,99) = .97$; $p = .41$) as predictors and HIV status as moderator were not significant.

Discussion

The aim of this study was to further examine the relationship between olfactory sensitivity and personality. This is the first time this has been investigated in men living with HIV, whose chemosensory skills and social adaptation are both believed to be affected by infection. It was suspected that both HIV+ and HIV- individuals with a more sensitive sense of smell are more focused on engaging in close relations with others, more caring, and more interpersonally warm than those with less sensitive olfaction. This effect was examined with the use of the model of agency and communion (Bakan 1966). While no relationship was observed between olfactory sensitivity and agency, those with higher scores on communion had significantly better score in olfactory sensitivity task. This effect can be explained with sensory filter theory (Croy et al. 2011), according to which the number of social odors processed by an individual is determined by the capacity of the olfactory system. A large amount of socially relevant information

Table 3 Spearman's correlation coefficients for olfactory and psychosocial variables

	Agency	Communion	Social activity	Satisfaction with social support
Olfactory sensitivity	0.14	.23*	.24*	.15

* $p < .025$

Fig. 1 Scatterplot of relationship between olfactory sensitivity and agency

contained in the received odors makes an individual more aware of their social environment, in turn, enhancing the development of communal personality traits. The observed effect was independent of HIV status. It appeared that HIV infection didn't affect the relationship between olfactory sensitivity and socially-relevant personality traits.

The second psychological measure analyzed, the Social Activity Questionnaire, assessed sociability more directly. Compared to communion, which is the general personality trait, items included in this inventory applied to more specific aspects of social functioning - how eager one is to engage in social activities, especially those involving helping and supporting others. The positive relationship between olfactory sensitivity and this behavioral tendency was significant only in the HIV+ subgroup. This may imply that engagement in interpersonal relations and staying socially active buffers the impact infection has on chemosensory functions.

On the other hand, satisfaction with received social support, measured with the Social Support Questionnaire, wasn't associated with olfactory sensitivity, either in HIV+ participants, or in healthy ones. This may be because the questionnaire doesn't assess basic dispositional personality characteristics, such as communion or tendency to eagerly engage in social activities, but rather involves the appraisal of a

particular social environment. While the level of satisfaction with social support is partially determined by an individual's personality (Sarason et al. 1983), it is also strongly affected by factors beyond their control.

The comparison of HIV-seropositive and HIV- participants had surprising results, since the groups didn't differ in olfactory sensitivity. The mean score on the olfactory task was higher, though not significantly, for HIV+ individuals. This result contradicts many previous reports on olfactory impairment in HIV infection (Graham et al. 1995; Razani et al. 1996; Mueller et al. 2002). A possible explanation is the use of very strict exclusion criteria in the current project. Infected individuals with impaired olfaction may have been not qualified to take part in the study. Another possible explanation is that the observed lack of difference was caused by the lower (though not significantly) mean age in the HIV-seropositive group relative to the HIV- group. The level of olfactory functions is highest between the age of 20 and 40 years, and then decreases steadily (Kovács 2004). In the current study, the mean age of the HIV+ group was just below 40 years, and the mean age of HIV- group was slightly higher than 40 years. HIV+ group consisted of lower proportion of heterosexual males vs. MSM compared to HIV- group. It was possible that MSM males perform better in olfactory tasks than heterosexual, thus the

Fig. 2 Scatterplot of relationship between olfactory sensitivity and communion

Fig. 3 Scatterplot of relationship between olfactory sensitivity and satisfaction with social support

observed lack of difference in olfactory sensitivity. The recent literature shows however, that it is gender nonconformity and sex-atypicality rather than sexual orientation (Nováková et al. 2013) that influence sexual orientation. However, to further address this issue, the multiple regression analysis was performed. It appeared that in analyzed group sexual orientation did not predict olfactory sensitivity significantly.

Limitations and Future Directions

One of the drawbacks in this study was the use of n-butanol odor. Though the substance is one of the most common odorants used in standardized assessments of olfactory sensitivity (Cain and Rabin 1989; Hummel et al. 1997), studies on relations between olfactory skills and social functioning call for the use of human body odors. Examining whether individuals with a higher sensitivity to sociochemosensory stimuli score higher on measures of socially relevant personality traits is an interesting direction for future research. It is also worth considering whether some personality traits moderate the effect of exposure to emotional information contained in body odor on the recipient's affective state and behavior (de Groot et al. 2012). Such emotional contagion may be stronger for individuals characterized by a higher level of

socially relevant personality traits (like agreeableness or communion) than for those less aware of others' feelings and needs.

Another important task for future studies is to examine how sex modifies the relationship between olfactory sensitivity and personality, both in the general population and in HIV-infected individuals. This study involved only male participants. Women, however, are believed to have generally better olfaction than men (Covington et al. 1999). It has been also proved, that females perform better in tasks involving social odors (Chen and Haviland-Jones 2000). It is interesting whether levels of agency and communion, personality traits considered to be stereotypically masculine and stereotypically feminine respectively (Abele 2003), mediate the effect of biological sex on olfactory performance. Moreover, the observed lack of significant correlation between odor sensitivity and eagerness to engage in social activities in the healthy group in the current study may be the result of all participants being male. It is thus important to include both male and female participants in future studies on relationships between odor sensitivity and socialization.

It is also important to take into the consideration the potential impact of HAART on olfactory functioning in HIV+ participants. Antiretroviral drugs penetrate into the central nervous system and, therefore, may impact olfactory functions. Several studies have reported disruptive effects of HAART on olfaction

Fig. 4 Scatterplot of relationship between olfactory sensitivity and eagerness to engage in social activity

and gustation (Fasunla et al. 2016; Raja et al. 2013). The participants of the current study, however, may be characterized with increased olfactory sensitivity. In recent literature, there is no evidence of positive effects of HAART on olfaction.

Conclusions

In conclusion, this study provides further data on the association between human olfaction and personality. Although the size of observed effects was small, the results are consistent with many previous studies. The capacity of the human olfactory system indeed appears to be related to the way individuals perceive the world and function in society. While the significance of odors for human psychological functioning is still far from being fully recognized, future exploration of this topic will surely bring important results, broadening knowledge of both personality development and the determinants of individual differences in social behaviors.

Funding The work was supported by grant no. 2012/06/M/HS6/00316 “The Effect of Age on Cognitive and Chemosensory Functions of the Brain in HIV Infection” awarded by the Polish National Science Centre (NCN).

Compliance with Ethical Standards

Conflict of Interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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