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Feature Article

FEATURE ARTICLE

Face Tuning in Depression

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Abstract

The latest COVID-19 pandemic reveals that unexpected changes elevate depression bringing people apart, but also calling for social sharing. Yet the impact of depression on social cognition and functioning is not well understood. Assessment of social cognition is crucial not only for a better understanding of major depressive disorder (MDD), but also for screening, intervention, and remediation. Here by applying a novel experimental tool, a Face-n-Food task comprising a set of images bordering on the Giuseppe Arcimboldo style, we assessed the face tuning in patients with MDD and person-by-person matched controls. The key benefit of these images is that single components do not trigger face processing. Contrary to common beliefs, the outcome indicates that individuals with depression express intact face responsiveness. Yet, while in depression face sensitivity is tied with perceptual organization, in typical development, it is knotted with social cognition capabilities. Face tuning in depression, therefore, may rely upon altered behavioral strategies and underwriting brain mechanisms. To exclude a possible camouflaging effect of female social skills, we examined gender impact. Neither in depression nor in typical individuals had females excelled in face tuning. The outcome sheds light on the origins of the face sensitivity and alterations in social functioning in depression and mental well-being at large. Aberrant social functioning in depression is likely to be the result of deeply-rooted maladaptive strategies rather than of poor sensitivity to social signals. This has implications for mental well-being under the current pandemic conditions.

Key words: depression, face pareidolia, face tuning, gender impact, non-face face-like images, social cognition

The latest COVID-19 pandemic demonstrates that unexpected and uncontrollable changes of the environment (isolation, public panic, and socioeconomic deprivation) lead to psychological distress and depression (Qiu et al. 2020). Major depressive disorder (MDD) is a foremost human blight, which is responsible for more years lived with disability than any other mental condition (Smith 2014). Yet depression is commonly underestimated, undiagnosed, and untreated because of stigma (and related to it dishonesty), lack of effective therapies, and inadequate mental-health resources. The Global Burden Disease Study pointed to the prevalence of MDD of about 163 million in 2017 (James et al. 2018). As only a diminishing part of MDD patients is treated in low- and mid-income countries, the disorder is not only an individual health issue but an essential socioeconomic problem (James et al. 2018). MDD is seen as a heterogeneous neuropsychiatric disorder with an etiopathogenesis comprising multiple biological, social, genetic, and psychobiological factors (Chirita et al. 2015). Stressful life events and circumstances, parental depression, interpersonal dysfunction, inappropriate guilt, and even "being female" are listed among robust risk factors of MDD (Hammen 2018), though child sexual abuse, domestic violence, and being in a "conflict country" are also among well-established factors. Core symptoms characterizing MDD are a low mood, anhedonia (inability to experience pleasure), and loss of energy (chronic fatigue). Moreover, affected individuals experience

insomnia (sleeplessness) or hypersomnia, a diminished ability to concentrate, low self-confidence, weight or appetite changes, and recurrent thoughts of suicide (Fried et al. 2016). MDD is considered the most common mental condition due to which suicide is committed (Bachmann 2018). In 2014, the prevalence of MDD had been reported to be the highest in Afghanistan and lowest in Japan (Smith 2014), though this may reflect the way in which the disease is experienced and diagnosed as well as cultural differences: for example, while standard diagnostic tools focus on mood, lack of motivation, and fatigue, Chinese individuals with depression often report stomach pain or headache. Although MDD drives public attention as well as attention of researchers and health services (e.g., our recent Pubmed search performed with a keyword "depression" resulted in 521 728 references), social and clinical relevance of MDD speaks for deeper investigations of the underlying mechanisms, e.g., for large human-genetic studies (Hyman 2014). Aside from neuroinflammatory and brain-morphological correlates of depressive symptoms, cognitive concepts have proven to be a valuable source of insights into the nature of MDD. For better understanding of MDD and improvement of therapeutic intervention, several models had been developed, among which are the Beck "cognitive triad" comprising negative views about 1) oneself ("*I'm ugly*"), 2) the outer world ("*No one values me*"), and 3) the future ("*Things can only get worse*") (Beck et al. 1979; Pössel and Smith 2020); the Seligman concept of *learned helplessness* in overcoming negative life experiences (Smallheer et al. 2018); and the theory of "critical life events" due to which depression is provoked by a loss or damage of self-definition and the lack of efficient interpersonal strategies to cope with it (Park et al. 2015; Strauss et al. 2018). Explicitly or implicitly, these models imply aberrant social cognition (our ability to understand emotions, desires, and drives of others) in MDD.

Although impairments in social cognition are characteristic features in many neuropsychiatric conditions such as autism and schizophrenia (Bora and Pantelis 2016), the impact of depression on social cognitive functioning is not well understood. MDD patients appear to be less severely impaired, and deficits in social cognition may be reversible (Wang et al. 2008; Bazin et al. 2009; Weightman et al. 2014). Social cognition has been shown to be crucial not only for a better understanding of MDD, but even more essential for specific screenings and treatments targeting social dysfunction (Menard et al. 2016; Knight and Baune 2018). Among indispensable components constituting social competence are body language reading and face perception (e.g., de Gelder et al. 2010; van den Stock et al. 2011; Kret and de Gelder 2012; Pavlova 2012; Pelphrey et al. 2014; van den Stock and de Gelder 2014; van den Stock et al. 2014; Tamietto et al. 2015; Di Giorgio et al. 2016; Di Giorgio et al. 2017; Pavlova et al. 2017a; Pavlova 2017b; Tillman et al. 2019). In MDD, the Reading the Mind in the Eyes Test (RMET) reveals difficulties in assessing the affective mental state, though negative emotional states are identified more accurately than in typical development, TD (Harkness et al. 2011; Wolkenstein et al. 2011; Cao et al. 2013). MDD individuals exhibit aberrant body language reading (Loi et al. 2013; Kaletsch et al. 2014). In the domain of face perception, most research focuses on processing of affective facial information. There is a paucity of evidence on face processing per se. In general, though controversial, the findings indicate that MDD individuals demonstrate increased sensitivity to negative expressions (sadness) as compared with positive (happiness) and exhibit a bias toward identification of negative emotions (anger and fear) and misidentification of positive emotions (Surguladze et al. 2004; Bourke et al. 2010; Demenescu et al. 2010; Csukly et al. 2011). Individuals with MDD need a greater stimulus intensity for identification of happy facial expressions and lower intensity for negative expressions (Joormann and Gotlib 2006; Gollan et al. 2010). Severity of depressive symptoms is negatively correlated with the ability to identify happy faces (Surguladze et al. 2004). The cognitive behavioral therapy improves recognition of happy facial expressions (Yilmaz et al. 2019). However, it remains unclear whether earlier stages of face processing such as basic facial schema (two eyes above mouth), assessment of the spatial relationship between facial features (configural processing), or holistic face processing (Piepers and Robbins 2012) are impaired in MDD individuals. Recent electroencephalographic (EEG) data suggests atypical face processing in MDD already at early stages: the N170 component of event-related potentials (ERPs) elicited by upright faces differ between patients and controls, whereas the difference is absent with display inversion (Yin et al. 2019).

Overall, it is largely unclear whether individuals with MDD exhibit deficits in the face sensitivity. Here we addressed this issue by applying a recently developed experimental tool, a set of images composed of food ingredients such as fruits and vegetables (Pavlova et al. 2015a; Pavlova et al. 2016a; Pavlova et al. 2016b; Pavlova et al. 2017b; Pavlova et al. 2018a; Pavlova et al. 2018b; Rolf et al. 2020). These Face-n-Food images border on the style of Giuseppe Arcimboldo, a virtuoso Italian painter known for imaginative portraits composed utterly of fruits, vegetables, and even roasted meat (Figs 1 and 2). The primary advantage of these images is that single components do not trigger face processing. In other words, on the Face-n-Food task, face tuning occurs spontaneously without being explicitly cued by familiar elements such as eyes. For seeing a face in these images, one has to establish spatial connections between single non-face components to shape a face schema. The other advantage of the task is the usage of unfamiliar images that is of value in clinical populations (Koelkebeck et al. 2015). In the present study, we intended to clarify 1) whether MDD individuals exhibit aberrant face tuning on the Face-n-Food task and 2) whether face tuning in MDD is gender specific. In addition, our desire was to elucidate whether face tuning in MDD patients is specifically related to other perceptual and cognitive abilities. With this purpose in mind, several additional tasks were administered that tap capabilities in perceptual organization and social cognition.

Method

Participants

Fifty-two participants (26 patients and 26 person-by-person matched controls) were enrolled in the study. Patients were recruited from in-patient units at the Department of Psychiatry and Psychotherapy, University Hospital, Eberhard Karls University of Tübingen, Germany. Twenty patients (13 females, 7 males) were involved in the first part of the study. Thirteen of them had been diagnosed with recurrent depressive disorder (ICD-10; F33): 4 patients with F33.1 (moderate form of recurrent depressive disorder) and 9 patients with F33.2 (severe form without psychotic symptoms). Seven patients had confirmed diagnosis of the MDD single episode (ICD-10; F32): 2 patients with F32.1 (moderate form), 3 patients with F32.2 (severe form without psychotic symptoms), and 2 patients with F32.3 (severe form with psychotic symptoms). Most of them had a pre-history of drugs [cannabis (6 patients), cocaine (3), lysergid—LSD (2),

Figure 1. Examples of the Giuseppe Arcimboldo style. "The Fruit Basket" or "Reversible Head with Basket of Fruit" (left), "The Gardener" (middle), and "The Cook" (right) by Giuseppe Arcimboldo, a virtuoso Italian painter best known for fascinating portraits composed of fruits, vegetables, and even roasted meat (https://commons.wikimedia.org/wiki/Giuseppe_Arcimboldo; public domain).

ecstasy (2)] and alcohol (15) and/or nicotine (8) consumption. At the time of examination, they were hospitalized for 39.10 ± 25.13 days, mean ± standard deviation (SD) (median, Mdn, 33 days; 95% confidence interval, CI, 27.34 to 50.86) and were in a post-acute phase. Except for three individuals, all patients were under either antidepressant (including selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors, SSRI/SNRI) and/or antipsychotic and/or sedative medical drug treatment. Twelve out of 20 patients had comorbidity (see Supplementary Material). Patients were aged 42.55 ± 13.33 years (Mdn, 47.5 years; 95% CI, 36.31 to 48.79), with an age range 19 to 58 years. Twenty control TD participants matched on a person-by-person basis for gender, age (42.80 ± 13.88 years; Mdn, 48 years; 95% CI, 36.86 to 48.74; with no difference between MDD and TD individuals; Mann–Whitney test, $U = 195.5$, n.s.), and education were recruited from the local community.

For the second part of the study aimed at clarification of gender effects on face tuning, we additionally recruited 6 males with MDD and 6 matched TD males. Four of these patients had confirmed diagnosis of recurrent depressive disorder (ICD-10; F33): one of them had a moderate (F33.1), and 3 a severe form without psychotic symptoms (F33.2). Two patients had confirmed diagnosis of MDD single episode (ICD-10; F32): 1 patient had a severe form without psychotic symptoms (F32.2), and 1 a severe form with psychotic symptoms (F32.3). A history of drugs (such as ecstasy) as well as alcohol and/or nicotine consumption was recorded in 4 patients. Two patients only reported neither taking drugs nor alcohol and nicotine in the past. At the time of examination, they were hospitalized for 24.67 ± 10.27 days and were in a post-acute phase. Except for one patient, all these patients were under either antidepressant and/or antipsychotic and/or sedative medical drug treatment.

Female patients were aged 41.15 ± 13.68 years (Mdn, 48 years; 95% CI, 32.89 to 49.42), and all male patients together (initial plus additional groups) were aged 40.15 ± 13.39 years with no difference in age between them (Mann–Whitney test, $U = 84$, n.s.). At the time of examination, females were hospitalized for 39.77 ± 23.97 and males for 31.77 ± 22.68 days (Mdn 24 days; 95% CI, 18.07 to 45.47) with no gender difference (Mann–Whitney test, $U = 65.5$, n.s.).

As performance on the Face-n-Food task and a digit span (DS) test (see below) requires language command of good proficiency, German as native language served as an inclusion criterion. Participants were run individually. All of them had normal or corrected-to-normal vision. None had previous experience with such images. The study was conducted in accord with the Declaration of Helsinki and was approved by the local Ethics Committee of the University of Tübingen Medical School, Tübingen, Germany. Informed written consent was obtained from all participants. Participation was voluntary, and the data was processed anonymously.

The Face-n-Food Task

The Face-n-Food task was administered to participants. This task is described in detail elsewhere (Pavlova et al. 2015a; Pavlova et al. 2016a; Pavlova et al. 2016b; Pavlova et al. 2017b; Pavlova et al. 2018a; Pavlova et al. 2018b; Rolf et al. 2020). In short, for this task, 10 images were produced that were composed of food ingredients, and to different degree resembled faces. Participants were presented with the set of images, one by one, in the predetermined order from the least to most resembling a face (images 1 to 10). This order was established in one of the previous studies with TD volunteers (Pavlova et al. 2015a). This fixed order of presentation had been used, since once seen as a face, Face-n-Food images are frequently processed with a face-dominating bias. On each trial, participants had to perform a spontaneous recognition task: they were asked to briefly describe what they saw. Their reports were recorded and then analyzed by independent experts. For further data processing, the responses were coded as either non-face (0) or face (1) report. No immediate feedback was provided. To avoid time pressure that can potentially cause stress and negative emotional and physiological reactions blocking cognitive processes in both patients and controls, there was no time limit on the task.

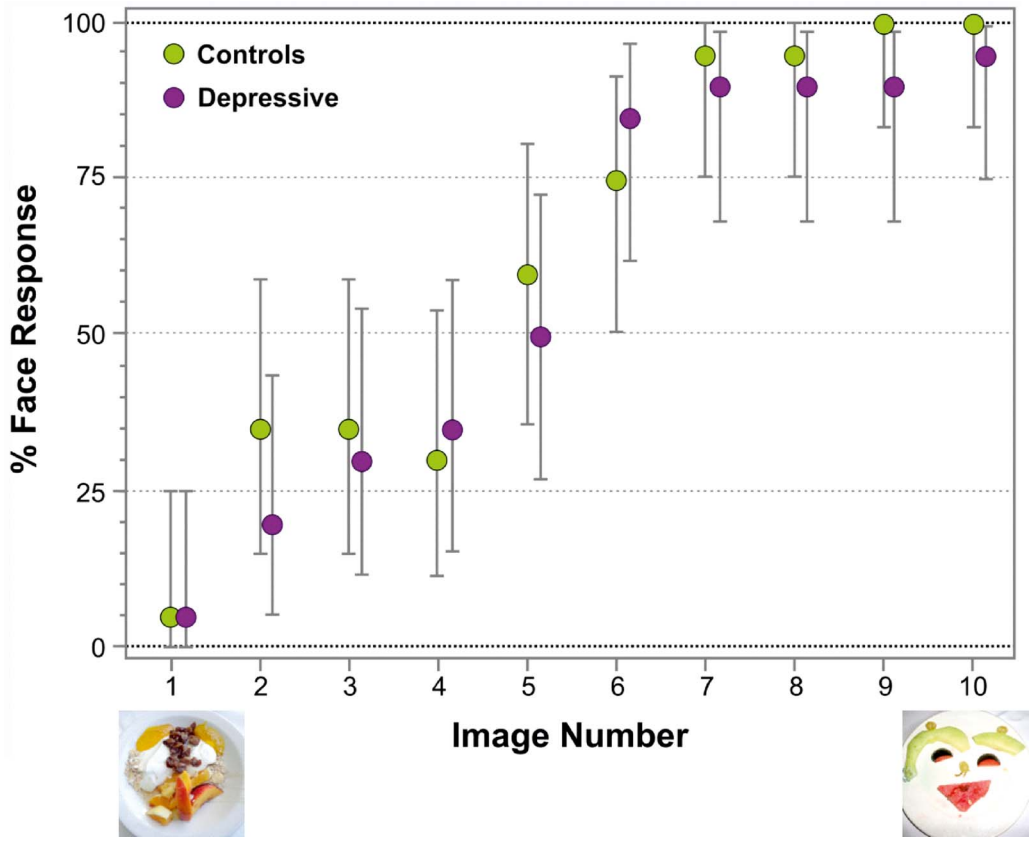

Figure 2. Percentage of face responses for each Face-n-Food image in patients with major depressive disorder, MDD (violet) and typically developing, TD, controls (green). The image number reflects its face resemblance (1, the least resembling a face, through 10, the most resembling a face images from the Face-n-Food task; these images had been first published in Pavlova et al. 2015a; doi: 10.1371/journal.pone.0130363; the Creative Commons Attribution [CC BY] license). Vertical bars represent 95% confidence interval, CI.

Additional Tasks

Similar to our previous study in schizophrenia (Rolf et al. 2020), three additional tasks were administered to both MDD patients and controls: 1) a digit span (DS) task tapping short-term working memory and attention load; 2) an event arrangement (EA) task, for which a participant has to re-organize a set of cards depicting an event in a comic-strip fashion (this task assesses the visual social cognition); and 3) a picture completion (PC) task (requiring identification of a missing piece of an object/scene) that examines visual perceptual organization. These tests are parts of the Wechsler Intelligenztest für Erwachsene (WIE), a battery based on the Wechsler Adult Intelligence Scale (WAIS-III) standardized and adapted to the German population (Von Aster et al. 2006). The tasks represent a well-established tool for neuropsychological assessment. With each participant, the whole testing procedure (the Face-n-Food task along with additionally administered tasks) lasted no longer than 30–45 min.

Data Analysis

All data sets were routinely analyzed for normality of distribution by using Shapiro–Wilk tests with subsequent usage of either parametric (for normally distributed data) or non-parametric statistics. For not normally distributed data sets, additionally to means and SDs, Mdns and 95% CIs are reported throughout the text.

Results

Face Tuning

Similar to previous studies with healthy participants and individuals with neurodevelopmental and psychiatric conditions (Pavlova et al. 2015a; Pavlova et al. 2016a; Pavlova et al. 2016b; Pavlova et al. 2017b; Pavlova et al. 2018a; Pavlova et al. 2018b; Rolf et al. 2020), MDD patients described a food-plate image either in terms of food compositions (non-face response, 0) or as a face (face response, 1). Thresholds for the face tuning (an average image number, on which a face response was reported for the first time) were comparable for MDD and TD groups, although one MDD patient completely failed on the Face-n-Food task. TD controls reported seeing a face for the first time on average on 4.30 ± 2.23 image, whereas MDD individuals gave the first face response on average on 4.53 ± 2.20 image. No difference between the groups in the face recognition thresholds was found ($t(37) = 0.685$, two-tailed, $P = 0.751$, n.s.).

Figure 2 represents percentage of face responses for each Face-n-Food image in MDD and TD individuals. As indicated

by multiple stepwise nominal logistic regression analysis, the effect of group (TD vs. MDD) on face tuning was not significant ($\chi^2(1) = 1.229$, $P = 0.268$, n.s.). Remarkably, there was no significant difference in face tuning between MDD and TD individuals for each of 10 images (Fisher's exact test: image 1, $P = 1.00$; 2, $P = 0.48$; 3, $P = 1.00$; 4, $P = 1.00$; 5, $P = 0.75$; 6, $P = 0.70$; 7, $P = 1.00$; 8, $P = 1.00$; 9, $P = 0.49$; 10, $P = 1.00$). As can be seen in Figure 2, dynamics of face recognition (the form and slopes of the fitted face recognition curves) were rather similar in both MDD and TD individuals. Both groups made substantial progress in face recognition from image 1 to 2 ($\chi^2(1) = 6.01$, $P = 0.014$), 4 to 5 ($\chi^2(1) = 4.06$, $P = 0.044$), and from image 5 to 6 ($\chi^2(1) = 5.49$, $P = 0.019$).

On all additional tests administered to participants, performance level of MDD patients did not significantly differ from TD individuals (DS task: MDD, 9.90 ± 3.26; TD, 11.70 ± 2.74; $t(38) = 1.538$, n.s.; EA task: MDD, 8.75 ± 2.81; TD, 10.40 ± 2.72; $t(38) = 1.533$, n.s.; PC task: MDD, 9.15 ± 2.87; TD, 10.05 ± 2.69; $t(38) = 0.493$, n.s.; two-tailed tests). Therefore, MDD patients were comparable with healthy controls in respect of these cognitive abilities.

As seen in Figure 3, in MDD, significant correlations were found between performance on the Face-n-Food task (face response rate) and scores on the PC task (Pearson product–moment correlation, $r(18) = 0.535$, $P = 0.015$), whereas in TD individuals the face tuning was linked to the scores on the EA test ($r(18) = 0.563$, $P = 0.01$). [Of note, the link between the face tuning and PC task had been confirmed in our ongoing study with another sample of MDD patients]. By contrast, in TD, no link was found between the face response rate and scores on the PC task ($r(18) = 0.175$, n.s.), and in MDD, no association occurred between the face response rate and EA task ($r(18) = 0.346$, n.s.). In both groups, no correlations occurred between the face tuning and scores on the DS test (MDD: $r(18) = -0.085$; TD: $r(18) = 0.068$, n.s.), which indicated that the face tuning examined by the Face-n-Food task and working memory/attentional load were not intrinsically connected with each other.

Gender/Sex Impact

The sex ratio of MDD individuals in the first part of the study was 1.86 (13 females to 7 males) that reflects differences usually reported in this clinical population (Kessler and Bromet 2013). As in young females, advantage in the face tuning had been previously reported on the Face-n-Food task (Pavlova et al. 2015a) and females are considered more proficient "at seeing faces where there are none" (Proverbio and Galli 2016), we examined whether female MDD patients possessed higher sensitivity to faces and, in this way, could camouflage possible deficits of the whole patients' group. Keeping in mind that the sample of females was almost twice as large as the male sample (comparison between such unequal samples may lead to paradoxical statistical outcomes), we additionally recruited 6 male patients and 6 matched controls (see Methods) and compared face responsiveness between 13 female/13 male MDD and 13 female/13 male TD individuals.

Female MDD patients gave the first face response on average on 4.69 ± 2.36 image, whereas male patients on 4.42 ± 1.98 image. The gender difference in face recognition thresholds was not significant ($t(23) = 0.697$, $P = 0.754$, two-tailed, n.s.). As indicated by the multiple stepwise nominal logistic regression analysis performed on the face response rate for each Face-n-Food image (Fig. 4), neither the effect of gender (females vs. males; $\chi^2(1) = 0.008$, $P = 0.929$, n.s.) nor the effect of group (TD vs. MDD; $\chi^2(1) = 0.071$, $P = 0.789$, n.s.) on face responsiveness was significant. The interaction of these factors was also not significant ($\chi^2(1) = 0.389$, $P = 0.943$, n.s.).

Discussion

By applying a novel tool, a recently developed Face-n-Food task (Pavlova et al. 2015a; Pavlova et al. 2016a; Pavlova et al. 2016b; Pavlova et al. 2017b; Pavlova et al. 2018a; Pavlova et al. 2018b; Rolf et al. 2020), we assessed the face sensitivity in patients with MDD. The key advantage of Face-n-Food images is that their single components do not promote face processing, and, therefore, for seeing a face one has to establish connections between non-face elements. The outcome indicates that 1) MDD individuals do not express lower face sensitivity: they are responsive to the Face-n-Food images and expose face recognition dynamics similar to TD individuals (Fig. 2); 2) neither in MDD nor in TD individuals do gender differences occur in the face tuning (Fig. 4); and 3) in MDD, the face tuning (face response rate) is linked to perceptual organization, whereas in TD, it is firmly associated with social cognitive abilities (Fig. 3). Therefore, the face tuning in MDD and TD individuals appears to rely upon different strategies and underwriting them brain networks.

Face Tuning in MDD and Other Neuropsychiatric Conditions

Previous work that implemented the Face-n-Food paradigm in Williams syndrome (Pavlova et al. 2016a), autistic spectrum disorders (Pavlova et al. 2017b), Down syndrome (Pavlova et al. 2018a), and patients with schizophrenia (Rolf et al. 2020) revealed substantial deficits in the face tuning in all these patient populations (for comparative analysis, see Rolf et al. 2020). In light of the present data, it appears arresting that performance level of MDD patients is comparable with TD controls in terms of 1) face tuning thresholds and 2) overall face recognition dynamics (Figs 2 and 4). Previous research on face-like non-face images indicates that for seeing a face where none exists, forming binding between even a couple of elements resembling eyes and mouth (a coarse face schema) is already sufficient (Omer et al. 2019). One possible explanation for intact face tuning in MDD is that this patient population may be particularly responsive to faces (as well as to other social cues) before the disease onset. Among other factors, this high sensitivity can contribute to disease progression. This assumption appears plausible, if one keeps in mind that individuals with high sensitivity to social signals and low psychological defense are more likely to become depressive. In the course of disease, high social tuning may decrease to (or even drop below) the level of non-affected individuals in general population. Yet, this assumption requires experimental proof that is challenging to deliver, since screening programs (if exist) do not usually involve rigorous psychophysical examination of social cognitive abilities.

The present study indicates that MDD individuals possess intact sensitivity to faces in non-face images. This outcome agrees with some previous studies showing that MDD patients are unhindered or less severely impaired on social cognition tasks: their deficits are more subtle than in other neuropsychiatric disorders (Wang et al. 2008; Bazin et al. 2009; Weightman et al. 2014). MDD patients are reported to be unimpaired on facial matching task (Matthews et al. 2008). Although some work reveals altered facial affect recognition (Surguladze et al. 2004; Bourke et al. 2010; Csukly et al. 2011), other groups do not

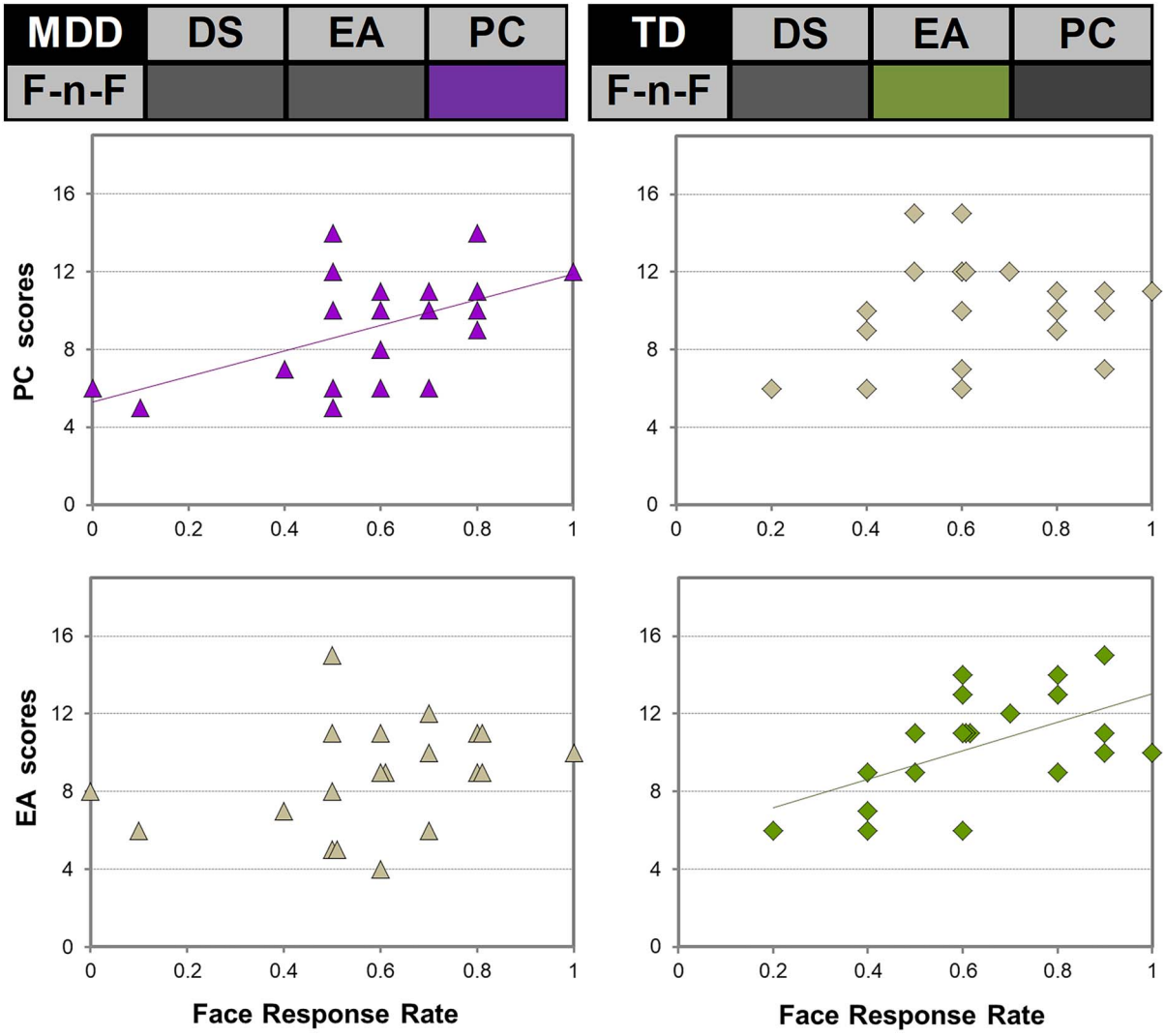

Figure 3. Relationship between the face response rate on the Face-n-Food task and scores on the digit span (DS), event arrangement (EA), and picture completion (PC) tests in MDD patients (left panel, triangles) and TD individuals (right panel, diamonds). In MDD, face response rate is positively linked with the scores on the PC test (violet; Pearson product–moment correlation, $r(18) = 0.535$, $P = 0.015$), whereas in TD, face response rate is associated with the scores on the EA test (green; $r(18) = 0.563$, $P = 0.01$). Correlation matrices on the top summarize these results.

support these findings. Patients with MDD do not show substantial deficits in processing of facial affect (Bediou et al. 2005; Joormann and Gotlib 2006; Gollan et al. 2010; Seidel et al. 2010), rating the valence of the masked facial expressions (Suslow et al. 2010) and in the theory of mind (ToM) comics test (Bazin et al. 2009). Moreover, it is suggested that MDD individuals are competent in perceiving and understanding of counterparts, but implement maladaptive strategies in dealing with social agents/signals and in overcoming challenging situations indicated by these signals. Therefore, even if facial emotion perception in MDD is described to be *biased*, this is more likely to be a result of deeply-rooted maladaptive cognitive concepts and strategies rather than *poor sensitivity* to social signals (Csukly et al. 2011). In other words, MDD patients can see what others see and feel, but they do not know or, better to say, do not have capacities for coping with this knowledge (Weightman et al. 2014). [Of note, social skills training that targets these maladaptive strategies may serve as an essential part of therapeutic interventions in MDD (Thase 2012).]

In a nutshell, this assumption dovetails well with the outcome of brain imaging. Hyperactivity of the ventral paralimbic regions and hypoactivity of the frontal regions (the limbic–cortical model of MDD) and abnormalities of the prefrontal cortex in communication with striatal and subcortical structures (the cortico-striatal model) point to deficient regulatory functions of the brain in depression (Mayberg 1997; Hamilton et al. 2012; Graham et al. 2013). MDD is accompanied by pivotal functional and structural abnormalities in several brain regions incorporating primarily the frontal cortex and cortico-limbic system [including the hippocampus, medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), posterior cingulate cortex/precuneus (PCC/PCu), amygdala, and caudate nucleus] (Rigucci et al. 2010; Hamilton et al. 2012; Graham et al. 2013). Most important, MDD individuals differ in terms of 1) abnormal functional connectivity between regions comprising the default mode network (DMN), which is active during mind-wandering and thinking about self and others, ACC–thalamus, ACC–insula, and

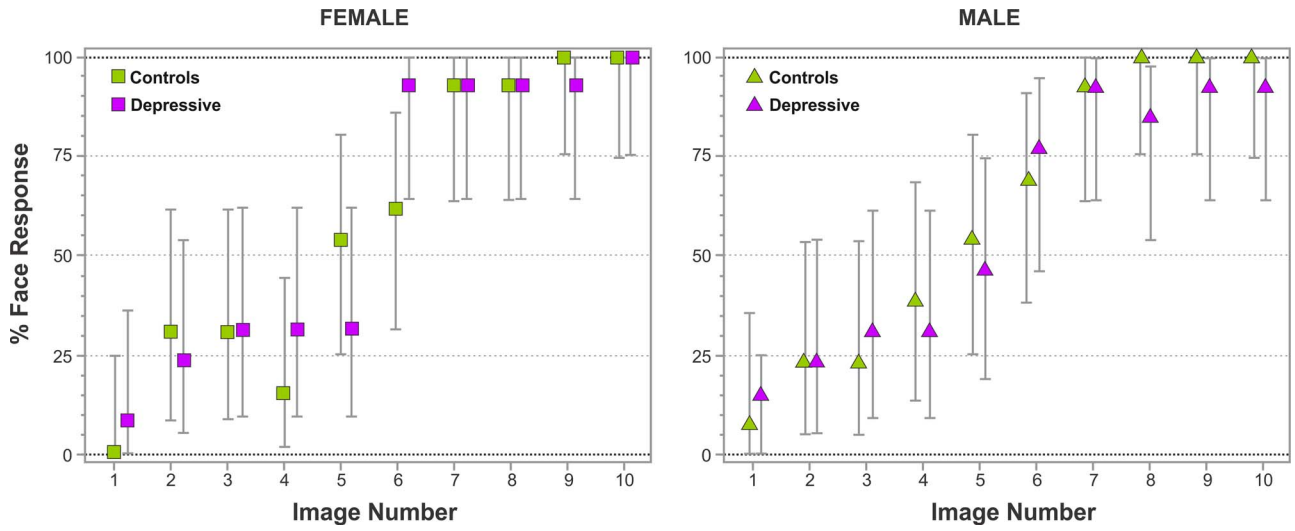

Figure 4. Percentage of face responses for each Face-n-Food image in female patients with MDD and controls (violet and green squares, respectively; left) and male MDD patients and controls (violet and green triangles, respectively; right). The image number reflects its face resemblance (1, the least resembling, through 10, the most resembling a face). Vertical bars represent 95% CI.

prefrontal–limbic–thalamic interplay; 2) structural covariance between prefrontal regions; and 3) anatomical connectivity in the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, posterior thalamic radiation, and corpus callosum (Rive et al. 2013; Gong and He 2015).

During facial affect processing in MDD, functional magnetic resonance imaging (fMRI) indicates alterations in brain connectivity in the neural circuits covering the ACC, amygdala, dlPFC, and orbitofrontal cortex (Stuhrmann et al. 2011) rather than dysfunction in the face-specific neural networks. These regions are known to be engaged in the reward system, emotion regulation, and decision making, aberrations of which are believed to be the core of this mental condition and may be considered as neurobiological markers of MDD (Hahn et al. 2011). On the other hand, EEG findings suggest atypical early stages of visual face processing (Yin et al. 2019). The multiplicity of ties between social cognition and functioning in depression most likely results from aberrations in different aspects of neural functions that range from the molecular up to neural circuits (Chaudhury et al. 2015).

The lack of differences in the face responsiveness between MDD patients and TD controls might be accounted for, at least partly, by SSRI/SNRI psychopharmacological treatment administered to some of patients at the time of examination. SSRI/SNRI medication is known to affect cognitive functions (e.g., to improve working memory) and perception and evaluation of affective faces and scenes (by decreasing sensitivity to fearful and other aversive images, while increasing a tendency to focus on positive images) in depression and healthy individuals (Castellano et al. 2020; Roberts et al. 2020; Zhang et al. 2020). Yet, whereas SSRIs reduce the amygdala response to fear and threat (for review, see Harmer and Cowen 2013), the opposite paradoxical effects are also reported: SSRI administration elevates resting-state perfusion in the right amygdala, increases bilateral amygdala activation to both positive and negative faces, and raises activation to fearful faces in the occipitoparietal, temporal, and prefrontal cortices (Di Simplicio et al. 2014). It is unclear, however, whether SSRI/SNRI affect the sensitivity to faces and other social signals at large. In the present study, no difference between MDD patients receiving SSRI/SNRI and those who were not under this pharmacological treatment was found not only for the face tuning (both face recognition thresholds and face response rate), but also for all additionally administered cognitive tests. Even more conclusive, no difference in face tuning (and other cognitive abilities) occurred between MDD patients *without* SSRI/SNRI treatment and TD controls person-by-person matched to them. Therefore, a possible influence of SSRI/SNRI medication on the present findings appears negligible.

Face Tuning and Other Cognitive Abilities

The outcome shows that although MDD and TD individuals do not differ in terms of the face sensitivity to non-face stimuli, face tuning in these populations differently relates to the EA test tapping visual social cognition and the PC test examining visual perceptual organization. Whereas in patients, face response rate is positively associated with the scores on the PC test, in healthy controls, the face tuning is related to the scores on the EA test. This suggests that although MDD and TD individuals do not differ in the face tuning demonstrating a rather similar performance level, this outcome may be achieved by recruiting diverse neural circuits. Indeed, previous brain imaging data of our lab, in particular, magnetoencephalographic (MEG) work revealing dynamics of brain activation, highlights group-specific (as well as sex-dependent) modes in the time course and topography of the neural circuitry underpinning visual processing of body motion (Pavlova et al. 2015b) and making perceptual decisions about social interaction when watching Heider-and-Simmel animations (Pavlova et al. 2010). These differences in brain activation occur even in the absence of behavioral differences. Overall, in patient populations, alterations of the brain response may prevent behavioral differences if they are maladaptive and in such a way foster an adaptive behavioral response. The differences in the brain response may be difficult to detect since at the level of brain topography, they may be rather subtle. Exploring the time course of brain activity helps in understanding atypical brain communication dynamics across

the neural networks making up the social brain (Pavlova 2017a, 2017b).

Face Pareidolia and Underpinning Brain Networks

Face pareidolia signifies tuning to a coarse facial schema in non-face images such as ink blots or clouds: a face schema is perceived even where no true face information exists (Evritt 2013). Recent findings suggest the existence of innate mechanisms for the face sensitivity and a kind of face predisposition (Di Giorgio et al. 2016; Reid et al. 2017). Infants and older children visually prefer face-like images, including Arcimboldo portraits, over similar configurations that do not contain facial schema or are inverted in the image plane (Kobayashi et al. 2012; Kato and Mugitani 2015; Shah et al. 2015; Guillon et al. 2016). Other species such as the rhesus monkey share face-detection machinery with humans (Nguyen et al. 2014; Taubert et al. 2017).

Clarification of the nature of face tuning in MDD speaks to specially tailored brain imaging work. Yet, even in TD individuals, the topography and communication of the brain networks underlying face tuning are largely unknown. In a nutshell, the findings demonstrate that 1) topography and time course of the neural circuits underpinning processing of real faces and face-like images are similar; pivotal activation includes the occipital cortices, fusiform face area (FFA), and inferior temporal brain regions (Liu et al. 2014; Proverbio and Galli 2016); and 2) corresponding brain activation is predominantly right-hemispheric. The right superior temporal sulcus (STS), a pivot of the social brain, segregates real faces from face-like configurations (Hadjikhani et al. 2009). Whole-brain fMRI analysis indicates that in a sample of predominately female TD adults, perception of faces and face-like images elicits similar activation in the occipital cortices, FFA, and inferior temporal areas (Akdeniz et al. 2018). EEG suggests that already 1- to 4-day-old newborns exhibit activation in the right-lateralized network engaging lateral occipito-temporal and medial parietal areas overlapping with the face-processing circuits in adults: the cortical network for processing of face-like images is likely to be active already at birth (Buiatti et al. 2019). The right hemispheric dominance is also found in processing of Arcimboldo-like images, which yield greater fMRI response in the occipito-temporal network (comprising the FFA) specialized for face processing, bilateral superior and inferior parietal cortices, and the right inferior frontal gyrus than Renaissance portraits and faces do (Boccia et al. 2015). In the left hemisphere, the amplitude of the face-sensitive N170 ERP component is larger for real faces, while in the right hemisphere the N170 component is comparable in response to Arcimboldo portraits and faces (Caharel et al. 2013). When contrasted with the same paintings inverted in the image plane, Arcimboldo portraits produce fMRI activation in the right FFA and posterior STS (Rossion et al. 2011). Individuals with premanifest Huntington's disease show a dramatic decrease in the N170 component of ERP elicited by the face-like images, and this decline is associated with the number of recognition errors, severity of apathy, and global cognitive abilities (Martínez-Horta et al. 2020).

Gender Specificity in MDD, Social Cognition, and Face Tuning

MDD is believed to have a skewed sex ratio: approximately twice as many females as males experience depression (Neitzke 2016; Salk et al. 2017), though depression in males can be overlooked and underestimated. Recent analyses indicate that (among other factors such as stress responsiveness) conformity to traditional masculine gender social norms and stereotypes may discourage men's help-seeking and affect the mode males experience and express depression (Seidler et al. 2016). Gender/sex differences in MDD have a multifactorial etiology [gender(sociocultural)/sex(neurobiological) factors continuously interact with each other across the lifespan], and determinants of gender differences are still far from being well understood (Piccinelli and Wilkinson 2000). The female preponderance in depression emerges by ages 13–15 years or even earlier (Salk et al. 2017) reflecting the impact of gonadal steroid changes at puberty (Parker and Brotchie 2010), and it remains constant till elderly (Salk et al. 2017). In the course of MDD, females tend to develop atypical MDD and coexisting anxiety disorders more often, whereas males are more likely to present comorbid addiction problems and are more prone to commit suicide (Schuch et al. 2014).

The question arises: how do gender differences in MDD affect social cognition? Only few experimental studies address this issue, and they are primarily related to processing of emotional information. When MDD individuals are asked to rate their tendencies to avoid or approach persons on the basis of information from their faces solely, women show greater avoidance than men (Seidel et al. 2010). Independently of disease severity, female patients exhibit a negative cognitive bias, whereas males demonstrate this bias only in the case of major depression (Wu et al. 2016). Healthy males show greater fMRI activation than females in the right superior frontal gyrus (SFG) after presentation of sad faces and in the right dorsomedial thalamus after presentation of neutral faces, whereas remitted MDD males display less activation in these regions than MDD females (Jenkins et al. 2018).

In the present study, we did not find any gender differences in the face tuning. Both men and women with and without MDD exhibited rather high sensitivity to a rough face schema in the Face-n-Food images. At first glance, this outcome contradicts previous findings. Indeed, female superiority has been observed by administering the Face-n-Food task in a homogeneous group of university students (Pavlova et al. 2015a). In females only, face resemblance in such images is positively associated with face likability (Pavlova et al. 2016b). Even subtle cultural impact can modulate gender differences: while young females from Germany and French-speaking part of Switzerland do not exhibit differences in the face tuning, Swiss males demonstrate higher face responsiveness than their German peers (Pavlova et al. 2018b). Although the female brain is reported to be more responsive to face-like images (like clocks or backpacks) with a greater activation in such areas of the social brain as the right STS and Brodmann area 22, sex differences are absent at earlier stages of face processing (Hadjikhani et al. 2009). The coarse face schema appears to be sex-independently hardwired in the brain. Overall, in MDD, gender/sex differences in social cognition are driven by higher-level modes of information processing, and their impact appears either negligible or secondary at earlier stages of face processing. This might serve as a possible explanation for the lack of gender differences in our study. Further work is required to explore sex differences in face tuning in health and disease at all levels of face processing. It appears challenging to detect sex differences in face processing up to their roots in the brain and untangle these roots affecting social behavior in MDD.

In summary, aberrant social functioning in depression is likely to be a result of deeply-rooted maladaptive cognitive

concepts and behavioral strategies rather than poor sensitivity to social signals such as faces. This outcome has implications for the mental health and social functioning under the current pandemic condition.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

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