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Face tuning in female and male individuals with major depressive disorder

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Kubon, Julian

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Dekan: Professor Dr. B. Pichler

1. Berichterstatter: Professorin M. Pavlova, PhD
2. Berichterstatter: Professor Dr. M. Giese
3. Berichterstatter: Professorin Dr. K. Kölkebeck

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Meinen Eltern, Johanna und Johann Kubon

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LIST OF ABBREVIATIONS

2AFC	Two-Alternative Forced-Choice
(95%) CI	(95%) Confidence Interval
ACC	Anterior Cingulate Cortex
AMY	Amygdala
AN	Affective Network
ANG	Angular (gyrus)
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
BA	Brodmann Area
BDI-II	Beck Depression Inventory - Second Edition
CAU	Caudate
CCN	Cognitive Control Network
COVID-19	Coronavirus Disease of 2019
CRP	C-Reactive Protein
CSD	Cross-Spectral Density
dACC	dorsal Anterior Cingulate Cortex
DC	Dorsal Caudate
DICS	Dynamical Imaging of Coherent Sources
DLPFC / dlPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DPSS	Discrete Prolate Spheroidal Sequence
DS	Down Syndrome
DS (test)	Digit Span (test)
EA (test)	Event Arrangement (test)
EEG	Electroencephalography
ERP	Event-Related Potential
FFA	Fusiform Face Area
FIE	Face Inversion Effect

fMRI	functional Magnetic Resonance Imaging
fNIRS	functional Near-Infrared Spectroscopy
FWE	Family-Wise Error
GABA(A)	Gamma-Aminobutyric Acid (receptor subtype A)
GMDS	Gotland Male Depression Scale
HIP	Hippocampus
HPA	Hypothalamic-Pituitary-Adrenal
HSD	Honestly Significant Difference
ICA	Independent Component Analysis
ICD-10	International Classification of Diseases, 10th Revision
IFG	Inferior Frontal Gyrus
IL-6	Interleukin 6
INS	Insula
LOC	Lateral Occipital Cortex
LSD	Lysergic acid diethylamide (German: Lysergsäure-diethylamid)
MDD	Major Depressive Disorder
Mdn	Median
MDRS	Male Depression Risk Scale
MEG	Magnetoencephalography / Magnetoenzephalographie
MNI	Montreal Neurological Institute
mPFC	medial Prefrontal Cortex
MTG	Middle Temporal Gyrus
MVOC	Medioventral Occipital Cortex
NA	Nucleus Accumbens
OFA	Occipital Face Area
OFC	Orbitofrontal Cortex
Oxy-Hb	Oxy-Hemoglobin
PC (test)	Picture Completion (test)
PCC	Posterior Cingulate Cortex
PCUN / PCu	Precuneus
PFC	Prefrontal Cortex
PHQ-9	Patient Health Questionnaire-9

pSTS	posterior Superior Temporal Sulcus
PUL	Pulvinar
RMET	Reading the Mind in the Eyes Test
RN	Reward Network
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SDT	Signal Detection Theory
SEM	Standard Error of the Mean
SFG	Superior Frontal Gyrus
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STS	Superior Temporal Sulcus
SZ	Schizophrenia
TCA	Tricyclic Antidepressant
TD	Typically Developing
TFR	Time-Frequency Representation
ToM	Theory of Mind
vACC	ventral Anterior Cingulate Cortex
WAIS-III	Wechsler Adult Intelligence Scale - Third Edition
WIE	Wechsler Intelligenztest für Erwachsene
WS	Williams Syndrome
YLD	Years Lost due to Disability

1 INTRODUCTION

1.1 Major depressive disorder

1.1.1 Prevalence and current challenges

Depression has emerged as one of the biggest challenges to societies all over the world. With a global prevalence of 264 million in 2017 [163 million affected by Major Depressive Disorder (MDD)], depression constituted the third leading cause of all-age years lost due to disability (YLDs): It amounts to a percentage of 14.3% with a still increasing tendency (absolute YLDs + 33.4% from 1990 to 2007 and + 14.3% from 2007 to 2017; James et al. 2018; Moreno-Agostino et al. 2021). As near to half of the world's population lives in countries with a psychiatrists-per-population ratio of no more than 2:100,000, there is a tremendous mismatch between affected individuals and the allocation of local mental health resources (Smith 2014). The prevalence rate of depression varies significantly between different countries and regions: Whereas Afghanistan reported the world's highest prevalence, the lowest value was determined for Japan (Smith 2014). Public awareness, social stigma, and the assignment of research funds have an impact on how depression is perceived, diagnosed, and treated.

The latest Coronavirus Disease of 2019 (COVID-19) pandemic fostered depression and anxiety right at the pandemic onset and with the implementation of lockdown restrictions (Qiu et al. 2020). Going in hand with an initial economic shock and social isolation, the pandemic aggravated depressive behavior, caused demoralization, and triggered suicidal ideation (Shader 2020; Unützer et al. 2020). However, after an initial peak, anxiety and depression levels declined in the first weeks after the lockdown start. This may be due to less severe restrictions on personal liberties in comparison to previous pandemics, a greater role of digital and inner space activities, and public anticipation of lockdown restrictions (Fancourt et al. 2021). Furthermore, the level of experienced distress depended on various external and internal variables: For example, female sex, young age, low education, poor income, and past mental health issues served as risk factors for

psychological distress (Hou et al. 2020; Özdin and Bayrak Özdin 2020; Fancourt et al. 2021).

1.1.2 Pathophysiology of depression

The pathophysiology of MDD comprises genetic, psychobiological, and socioeconomic factors. The heritability rate is estimated to be 30–50% (Sullivan et al. 2000) with evidence for an even tighter link in severe depression (McGuffin et al. 2007; Menke et al. 2012). Clinical heterogeneity of depression results most likely from a polygenetic background with many small effect-size genes contributing to the condition's onset and maintenance (Shadrina et al. 2018; Kendall et al. 2021). Yet, epigenetics and genome-wide association studies further need to untangle the contribution of genes and the environment (Hyman 2014; Shadrina et al. 2018; Mitchell et al. 2021). At the molecular level, one key concept underlying MDD is the monoamine deficit hypothesis: It implies a reduced synaptic communication via the monoamine neurotransmitters serotonin, noradrenaline, and dopamine (Perez-Caballero et al. 2019). As these transmitters have a central role in decisional control, motivation, and the reward system, a reduced synaptic concentration fosters depressive symptoms. Thus, a broad range of antidepressants [e.g., tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)] counteract the monoaminergic deficit. Nevertheless, given the delayed clinical effect of antidepressants and response rates of only around 50%, the monoamine deficit hypothesis does not fully explain the molecular basis of MDD (Perez-Caballero et al. 2019). Neurosecretory and hormonal imbalance may further include (i) the hypothalamic-pituitary-adrenal (HPA) axis (i.e., elevated level of glucocorticoids, reduced volume of the hypothalamus, and deficient negative feedback loops; Boku et al. 2018), and (ii) disruptions of circadian and hormonal rhythms [i.e., decreased and phase-shifted melatonin signaling, downregulation of hypothalamic orexin secretion, and disturbances in circadian oscillators of the suprachiasmatic nucleus (SCN); Mendoza 2019]. The latter findings dovetail with clinically observed disruptions of the circadian rhythm as well as insomnia or hypersomnia. Earlier, inflammatory mechanisms were discovered as another concept of MDD pathophysiology: These neuroinflammatory processes include activation of microglia, vascular damage, excitotoxicity, and increased levels of

inflammation markers in blood and the cerebrospinal fluid [e.g., C-reactive protein (CRP) and Interleukin 6 (IL-6); Haapakoski et al. 2015; Troubat et al. 2021]. Although neuroinflammation has an established role in the understanding of neurodegenerative disorders with secondary depressive symptoms (including *Morbus Parkinson* and *Morbus Alzheimer*), its influence on primary depression needs to be further investigated.

Brain alterations in MDD

MDD patients show distinct alterations of brain networks. The *limbic-cortical componential model* of depression proposes underactivity of a *dorsal compartment* [comprising the dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), inferior parietal cortex, and striatum] and overactivity of a *ventral compartment* including paralimbic and subcortical regions [brainstem, HPA axis, insula (INS), and the subgenual area; Mayberg 1997]. Whereas hypoactivity of the dorsal compartment may drive attentional and cognitive symptoms (e.g., apathy, attention deficits, and impairment of executive functions), hyperactivity of the ventral compartment is thought to reflect somatic and vegetative symptoms of MDD.

Another model of depression emphasizes the interplay of cortical, thalamic, and subcortical structures (*integrative neural model of heightened salience*; Hamilton et al. 2012): Based on this, MDD is characterized by higher baseline activation of the pulvinar (PUL; responsible for emotional attention) and over-reactivity of the salience network comprising INS, amygdala (AMY), and dACC. Due to lower striatal dopamine concentrations, sensory information may insufficiently rise to the dorsal caudate (DC) and DLPFC (contextualization and reassessment of emotional input). Thus, MDD patients lack adequate evaluation of affective content (*under-reactivity* of DC and DLPFC), and, at the same time, deal with viscerally superimposed input (*over-reactivity* of salience network). Furthermore, MDD patients exhibit a deficit in *top-down control* [reduced connectivity between anterior cingulate cortex (ACC) and AMY], decreased grey-matter volume and glial density in the hippocampus (HIP) and prefrontal cortex (PFC) (associated with memory impairments and other cognitive symptoms of MDD), and abnormal functioning of the nucleus accumbens (NA; a key structure of the reward

system) (Krishnan and Nestler 2008; Leistedt and Linkowski 2013; Chiriţă et al. 2015; Mavridis 2015). Later connectivity analyses have refined dysconnectivity in MDD and its associations with clinical features: In a nutshell, there is evidence for increased connectivity in the default mode network (DMN) and affective network (AN), which is linked to rumination and dysphoria. The other way around, hypoconnectivity within the reward network (RN) and cognitive control network (CCN) is associated with anhedonia and disturbances in cognitive functioning (Li et al. 2018, see **Figure 1**).

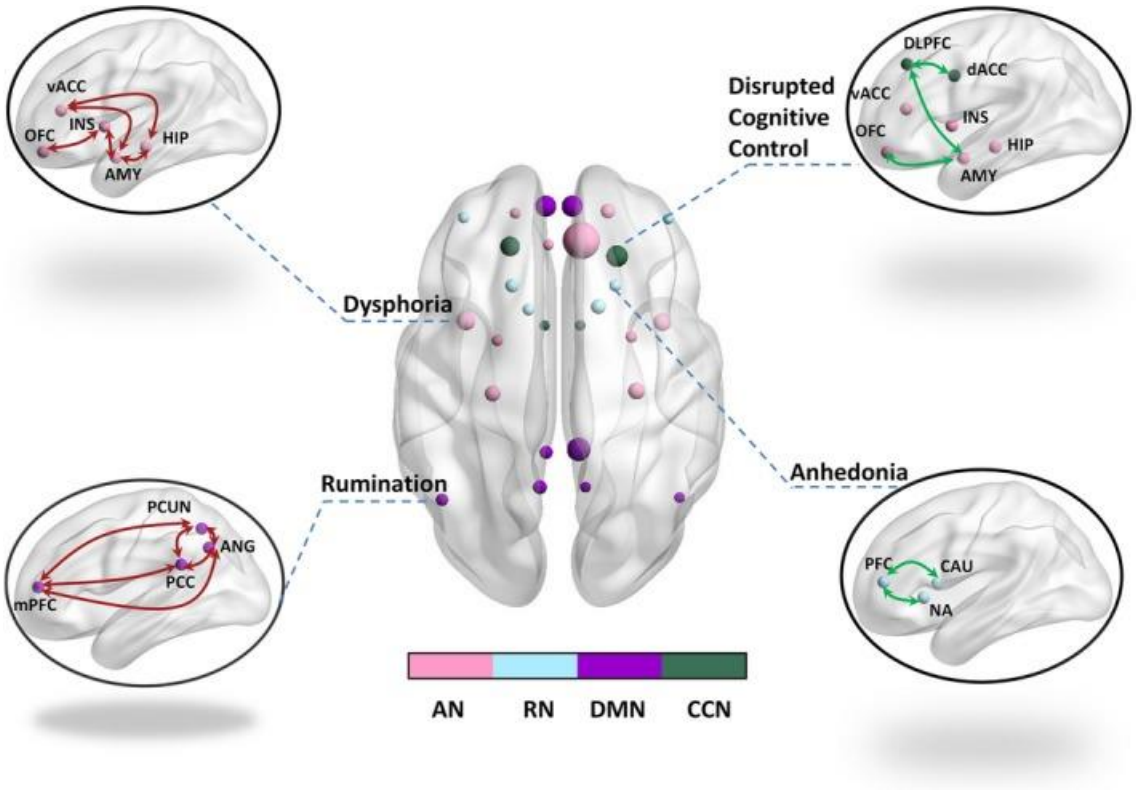

Figure 1. Dysconnectivity in MDD. Brain network models of depression suggest hyperconnectivity (red arrows) of an affective network (AN, pink blobs) and default mode network (DMN, magenta blobs) associated with dysphoria and rumination. Conversely, hypoconnectivity (green arrows) of a cognitive control network (CCN, green blobs) and reward network (RN, blue blobs) is thought to underlie impaired cognitive control and anhedonia. AMY, amygdala; ANG, Angular; CAU, caudate; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insula; mPFC, medial prefrontal cortex; NA, nucleus accumbens; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PCUN, precuneus; PFC, prefrontal cortex; vACC, ventral anterior cingulate cortex. From Li et al. 2018; Copyright © 2018 John Wiley & Sons Ltd, reprinted with permission of the publisher.

Bridging the gap between the molecular, structural, and clinical-behavioral reality of depression has been a major challenge for cognitive neuroscience. Several approaches exist that aim to understand MDD from the (social) cognitive perspective: Among these are (i) *Beck's cognitive triad model* (i.e., a negative mindset about oneself, the outer environment, and the future; Beck et al. 1979), (ii) the model of *learned helplessness* (i.e., passive and inadequate coping strategies following experienced helplessness; Seligman 1972), (iii) the cognitive vulnerability-stress (diathesis-stress) model (i.e., determination of MDD by an interaction of external events and internal vulnerability; Colodro-Conde et al. 2018), and (iv) the theory of *critical life events* due to which major and unexpected life events (e.g., illness, financial loss, separation) trigger depressive symptoms by damage of self-definition (Strauss et al. 2018). Directly or indirectly, these models assume aberrant social cognition in MDD.

1.1.3 Clinical manifestation and diagnosis

Core symptoms of depression based on the International Classification of Diseases, 10th Revision (ICD-10) are a depressed mood, lack of interest, and increased fatigability (Dilling et al. 2015). In addition, affected individuals may experience a broad range of emotional (feelings of worthlessness or guilt), vegetative (insomnia or hypersomnia, appetite, and weight changes), and cognitive (reduced ability to think and concentrate, psychomotor agitation or retardation) symptoms (Malhi and Mann 2018). Depressive episodes can further be specified by severity (mild/moderate/severe), time course (single episode/recurrent), onset (early/late), remission status, and characteristic features of the episode (e.g., additional mood-congruent psychotic symptoms). Several questionnaires were developed to guide the screening and diagnosis of MDD, e.g., the Patient Health Questionnaire-9 (PHQ-9) and the Beck Depression Inventory - Second Edition (BDI-II), which aim to combine clinical practicability, accuracy, and high sensitivity (Wang and Gorenstein 2013; Levis et al. 2019). However, it is important to note that these tools do not cover the broad range of depression subtypes as well as cultural differences. For example, Chinese individuals with MDD often report a pattern of somatization (e.g., headache and stomach pain), which may be overlooked by diagnostic tools focusing on

classic depressive symptoms as mentioned above (Ryder and Chentsova-Dutton 2012; Smith 2014).

1.1.4 Treatment concepts and prognosis

There is a broad spectrum of psychotherapeutic and pharmacological interventions, which aim at remission of MDD symptoms as well as psychological, social, and professional rehabilitation of affected individuals (Malhi and Mann 2018; Park and Zarate 2019). These treatment strategies are directed toward dysfunctional social cognitive patterns and negative biases in MDD. Among the best evidence-based psychotherapeutic interventions are (i) cognitive behavioral therapy, which focuses on the patients' negative self-concepts and thoughts, and (ii) interpersonal therapy, which addresses interpersonal conflicts in social situations (Cuijpers et al. 2011; Gautam et al. 2020). However, despite elaborate treatment strategies, MDD remains a menace to mental well-being: Although the cumulative recovery rate of MDD patients within one year was reported to be as high as 70%, most patients (up to 80%) experience at least another episode in their lifespan (Penninx et al. 2011; Malhi and Mann 2018).

1.2 Female and male depression

Depression shows a female preponderance with around twice as many females being affected by MDD as males (Salk et al. 2017). Meta-analyses report the *sex* (neurobiological factors) */gender* (a social construct related to social norms, identification, and roles) *gap* to arise earlier than previously estimated (around the age of 12 years), peak during adolescence, and, after contracting again, be stable during adulthood (Faravelli et al. 2013; Salk et al. 2017). According to these authors, the sex/gender disparity in adolescence may reflect unfavorable effects of early puberty on females, higher stress levels, and greater negative cognitive styles (the *cognitive vulnerability-stress model*). Nevertheless, the exact origin of female preponderance in depression is still a matter of debate. Underlying factors may further include rumination (i.e., perseverative cognitive style focused on negative feelings and situations), elevated

neuroticism, and deficient positive affectivity (Afifi 2007; Kuehner 2017). At the hormonal level, the findings are far from conclusive. In brief, (i) girls show higher vulnerability toward the activating effects of sex steroids during puberty, (ii) some women show higher susceptibility toward physiological hormonal fluctuations (premenstrual, peripartum, and perimenopausal depressive symptoms), and (iii) atypical depression characterized by HPA axis hypoactivity is more common among women (Kuehner 2017). Sex hormones profoundly impact the cellular and neuronal representation of social behavior. They influence neural pathways involved in the processing of aversive stimuli (fear and threat), modulate HPA axis responsiveness to stressors, and impact cellular transduction via genomic and non-genomic pathways (Slavich and Sacher 2019).

Considering clinical phenotype, females show greater symptom severity and more often report impaired sleep and energy. Furthermore, they experience greater gastrointestinal symptoms and higher interpersonal rejection sensitivity (i.e., preoccupation with real/perceived rejection/failure; Marcus et al. 2005). Affected individuals have an elevated risk of comorbid anxiety, somatoform disorder, bulimia, and atypical depression (i.e., characterized by early onset, hypersomnia, and weight gain; Altemus et al. 2014). In contrast, males tend to exhibit externalizing symptomatology (including risk-taking, anger, and irritability), which triggers substance misuse and poor impulse control (Oliffe et al. 2019). Although most suicide attempts in the course of depression are conducted by females, men account for the majority of completed suicides. This calls for a better understanding of male MDD and poses a challenge for surveillance of suicidal ideation in medical primary care facilities (Blashki et al. 2006). So far, adapted psychometric testing, e.g., the Gotland Male Depression Scale (GMDS) and the Male Depression Risk Scale (MDRS) (Zierau et al. 2002; Rice et al. 2013; Oliffe et al. 2019) has been established, which addresses prototypic and externalizing symptoms and may help to identify men at risk for suicide (Rice et al. 2019). Notably, screening for both *traditional* and *male-type* symptoms of depression may even eliminate the sex/gender gap in MDD prevalence. Therefore, some authors argue that this gap is due to a lack of male detection rather than higher female vulnerability (Martin et al. 2013).

Gender norms and masculine ideals (e.g., "*big boys don't cry*") determine how male depression is perceived, diagnosed, and treated. Situations related to loss of status or relationship as well as financial difficulties are reported to trigger depression in men (Ogrodniczuk and Oliffe 2011). Once affected, men are reported to ascribe depressive symptoms to physical rather than mental illness and, as these symptoms contradict masculinity ideals, experience them with even greater intensity (Seidler et al. 2016). In this context, social stigma, self-stigma, and traditional male gender ideals are boundaries for professional help-seeking. Thus, instead of actively seeking professional support, men develop a maladaptive compensation and avoidance strategy (e.g., through social withdrawal, excessive workload, and substance misuse). Men were shown to self-report lower levels of neuroticism and agreeableness, which poses the risk for therapists to underestimate the severity of depression (Nikolic et al. 2020). When already in contact with the professional setting, affected males prefer group-based, short-time therapeutic interventions focused on self-empowerment, trust, collaboration, problem-solving, and usefulness in daily situations (Seidler et al. 2016; Oliffe et al. 2019).

Taken together, recent decades have shed light on the societal and clinical implications of male MDD. However, despite growing interest (a Pubmed search performed recently by our working group with the keywords 'male depression' produced more than 300,000 results), male depression remains under-investigated and, with even greater implications for affected individuals, often undiagnosed (Swetlitz 2021).

1.3 Social cognition

Social cognition (i.e., perception and understanding of social properties and traits of others such as intentions, drives, emotions, and dispositions) is of tremendous value for a variety of daily life activities (Pavlova 2012; Pavlova et al. 2022). How do we know whom to trust or who is attracted to us? Such judgments are vital to successful social interaction. Social cognitive processes include (i) social perception (i.e., processing of social cues), (ii) social understanding (i.e., illuminating others' affective and cognitive processes), and (iii) social decision-making, in which own drives and others' intentions are combined to plan adaptive behavior (Arioli et al. 2018).

Next to verbal social cognition and interaction, non-verbal social cognition is essential for adaptive behavior. Faces and bodies provide us with a wealth of socially relevant non-verbal information. Body language reading and face recognition are indispensable components of non-verbal communication and constitute a core of social competence (de Gelder 2009; Kret and de Gelder 2012; Pavlova and Sokolov 2022a; Pavlova and Sokolov 2022b). The other important advantage of non-verbal sources of social information is that whereas verbal information flow is believed to be easily kept under control, face and body language often reveal our true feelings. *Body language reading* and *face processing* entail tightly packed, dynamic, and valuable social information (Adolph and Hoch 2020; Beaudoin and Beauchamp 2020; Isernia et al. 2020). Whereas vital for effective communication in typically developing (TD) individuals, aberrancies in face processing and body language reading are common in many mental disorders including MDD, bipolar disorder, schizophrenia (SZ), and autism spectrum disorder (ASD) (Kaletsch et al. 2014b; Vaskinn et al. 2016; Bi and Fang 2017; Pavlova et al. 2017b; Lee and Van Meter 2020; Rolf et al. 2020; Romagnano et al. 2022).

1.3.1 Face perception and face pareidolia

Face perception includes the identification of face elements, their spatial relationship as well as holistic facial representation. Strikingly, even a rough face scheme is sufficient for perceiving a face: Participants rated mouth and eyes as the most valuable facial features in terms of face detection, and removing these features significantly impeded face-likeness (Omer et al. 2019). Configural models for face processing distinguish *first-order facial features* (e.g., two eyes, mouth), which are processed independently, *second-order features* drawn from the spatial arrangement of two first-order features (e.g., the relationship between eyes and eyebrows), and *higher-order features* (e.g., age) based on numerous first- and second-order features (Piepers and Robbins 2012; Rhodes 2013).

Face pareidolia represents the ability to see faces in configurations of clouds, ink blots, and landscapes where no real face information is present. Already 10-12-month-old infants preferentially direct their gaze toward the mouth region of pareidolic faces (Kato and Mugitani 2015). The sensitivity to a coarse face scheme appears early in development

and is believed to remain hardwired in the brain (Vallortigara 2021). Strikingly, face pareidolia is not an exclusively human phenomenon, but is observed in the Rhesus monkey, chicks, and even tortoise hatchlings without parental care, which advocates the existence of a general inborn mechanism for detecting animacy (Rosa Salva et al. 2011; Taubert et al. 2017; Versace et al. 2020; Taubert et al. 2022). Deficits in face pareidolia may be caused by alterations in the visual *sensitivity* (i.e., a greater discrimination ability between non-faces and faces) and/or in *decision criterion* (related to a general bias to see faces either everywhere or nowhere; Zhou and Meng 2020). Within the signal detection theory (SDT) framework (Macmillan and Creelman 2005), fewer face pareidolia reports may be caused either by a more conservative decision criterion, a lower sensitivity, or a trading between them (Romagnano et al. 2022).

1.3.2 Brain networks engaged in face processing

Face-selective brain regions have been localized in the inferior occipital gyrus [occipital face area (OFA)] and in the posterior and lateral portions of the fusiform gyrus [fusiform face area (FFA); Grill-Spector et al. 2017; Cohen et al. 2019; Tsantani et al. 2021]. Although these regions receive their input from downstream occipital visual areas, a simple hierarchical model of face processing is insufficient. Instead, vertical white matter tracts toward the attention network (suggesting *top-down modulation*), subcortical connections to the PUL and AMY in primates, and bypass connections (which could endure disease and injury) reveal a highly complex network (Grill-Spector et al. 2017). Together, the FFA, OFA, and posterior superior temporal sulcus (pSTS; a key area of the social brain) constitute a *core network* of face processing (Bernstein and Yovel 2015). While this network shows bilateral activation in children, it gains right-hemispheric lateralization during maturation (Hildesheim et al. 2020). Hemispheric preponderance may further be related to different aspects of face processing itself [categorical (face/non-face; right FFA) vs. graded (face similarity; left FFA) processing; Meng et al. 2012]. Strikingly, females present less dominant lateralization, which may account, at least, in part, for their reported superiority in face-related tasks (Bourne 2005; Zhou and Meng 2020).

Along with the *core network*, there is an *extended network* of face processing, which deals with contextualization and assessment of facial information. It includes (i) the anterior temporal lobule (integration of person-related facial information), (ii) the AMY and associated limbic system [INS, orbitofrontal cortex (OFC), and cingulate; emotional relevance of facial input], and (iii) the ventrolateral PFC (top-down control) (Collins and Olson 2014; Rapcsak 2019; Sellal 2022).

Studies investigating the neuronal pathways of *face pareidolia* are sparse, and the outcome remains controversial. The existing data point to similar networks engaged in the processing of face-pareidolia as compared to real faces. Functional magnetic resonance imaging (fMRI) activation was observed in the early visual areas as well as in the FFA and PFC (Akdeniz et al. 2018). Magnetoencephalography (MEG) revealed a response peak at around 165 ms for real faces and face-like objects in the FFA, but only real faces produced an even earlier peak at 130 ms (Hadjikhani et al. 2009). Whereas real faces elicited an earlier and larger amplitude N170 event-related potential (ERP) component, the vertex positive potential exhibited higher amplitude and greater latency for pareidolia as compared to real faces (Akdeniz 2020). Thus, despite similar networks at the topographic level, the time course may differ between the processing of real faces and face-pareidolic stimuli. This needs further investigation, as time is a critical variable for the investigation of functional brain networks (Pavlova 2017a).

In a nutshell, brain imaging data in TD individuals indicate that (i) face processing engages a right-lateralized occipitotemporal core network (FFA, OFA, pSTS), (ii) this core network is interconnected with the brain areas of the extended face network (contextualization and assessment of facial input), and (iii) face pareidolia appears to recruit topographically similar neuronal pathways as compared to the processing of real faces.

1.4 Face perception in MDD

Examination of social cognitive abilities is crucial for understanding, treatment, and remediation of MDD. Affected individuals displayed deficits in the Reading the Mind in the Eyes Test (RMET), performed poorer on cognitive theory of mind (ToM) tasks, and

exhibited aberrancies in body language reading (Wang et al. 2008; Zobel et al. 2010; Loi et al. 2013). However, these findings are far from conclusive, and other groups point to more subtle deficits and reversibility following antidepressant treatment (Bazin et al. 2009; Harmer et al. 2009; Weightman et al. 2014). Regarding face processing, most studies on depression focus on the recognition of *facial affect*. In essence, it was shown that MDD individuals (i) exhibit a negative bias in facial valence assessment (i.e., MDD patients evaluate facial expressions more negatively), (ii) misattribute intensity of stimuli (e.g., higher intensity perceived in sad and harsh facial expressions), and (iii) show extended response time toward facial affect (Surguladze et al. 2004; Gollan et al. 2008; Csukly et al. 2011; Weightman et al. 2014). The recognition accuracy of happy faces decreases with the severity of depression (Surguladze et al. 2004). Furthermore, depressed individuals exhibited difficulties in rating ambiguous, subtle, and neutral facial expressions (Leppänen et al. 2004; Bourke et al. 2010; Gollan et al. 2010). The latter finding is highly relevant since situations of social ambiguity are thought to impose emotional distress on individuals with MDD (Everaert 2021).

However, despite numerous studies on facial affect processing, evidence on the face sensitivity *per se* remains scarce. Further research needs to be directed toward the investigation of face tuning itself to assess sensitivity toward social signals within this patient population.

1.5 Goals

The present work aimed to investigate face processing in female and male individuals with depression. MDD patients are reported to exhibit deficits in several aspects of non-verbal social cognition including body language reading and face perception. Yet, despite a bundle of research on *facial affect* recognition, evidence on face processing *per se* is scarce. To investigate face tuning, we used the Face-n-Food face-pareidolic images (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; Pavlova et al. 2021). These Arcimboldo-like images consist of food ingredients and, to a varying degree, resemble faces (**Figure 2**). The key advantage of the Face-n-Food images is that their single components do not trigger face processing. In our initial behavioral study, we intended to

clarify (i) whether MDD patients show shortages in face tuning, (ii) whether face tuning in MDD is sex/gender-specific, and (iii) whether face processing allies with specific visual-cognitive abilities.

Figure 2. Face pareidolia and Face-n-Food images. Face-pareidolic portrait 'The Gardener' of the virtuoso Italian painter Giuseppe Arcimboldo (left; from Wikimedia Commons: Free media resources, public domain). Two examples of the Face-n-Food images, from the least (middle) to the most face-resembling image (right). Images are shown with canonical upright orientation (top panels) and with display inversion (bottom panels), which significantly impedes face impression. From Pavlova et al. 2015a; Creative Commons Attribution License [CC BY].

Our results provided evidence for unhindered face tuning in MDD, but possibly different underlying cognitive strategies (Kubon et al. 2021). Based on this, our next step was to explore the brain networks underpinning face tuning in MDD.

With this purpose in mind, we used MEG, a non-invasive brain imaging modality providing a high resolution over space and time. We set a focus on male depression because (i) this clinical group is currently under-investigated, and (ii) exploration of brain networks by means of brain imaging, in particular, MEG, requires a homogenous group

of participants. We intended to clarify the following issue: whether, and, if so, how, brain networks involved in the processing of face-like images are altered in male depression (Kubon et al. 2023). To this end, we analyzed gamma oscillatory activity during the presentation of upright and inverted Face-n-Food images. Display inversion does not only substantially impede face pareidolia (Pavlova et al. 2020) but serves as an adequate control condition as the intra-stimulus content is comparable for both orientations.

2.1 Face Tuning in Depression

Julian Kubon, Alexander N. Sokolov, Rebecca Popp, Andreas J. Fallgatter, and Marina A. Pavlova

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FEATURE ARTICLE

Face Tuning in Depression

Julian Kubon[1], Alexander N. Sokolov[1], Rebecca Popp[1], Andreas J. Fallgatter[1,2,3] and Marina A. Pavlova[1]

[1]Department of Psychiatry and Psychotherapy, Medical School and University Hospital, Eberhard Karls University of Tübingen, 72076 Tübingen, Germany, [2]LEAD Graduate School & Research Network, Eberhard Karls University of Tübingen, 72076 Tübingen, Germany and [3]German Center for Neurodegenerative Disorders (DZNE), Medical School and University Hospital, Eberhard Karls University of Tübingen, 72076 Tübingen, Germany

Address correspondence to Prof. Marina A. Pavlova, Department of Psychiatry and Psychotherapy, Medical School, Eberhard Karls University of Tübingen, Calwerstr. 14, 72076 Tübingen, Germany. Tel: +49 7071 2981419; Fax +49 7071 2925266; Email: marina.pavlova@uni-tuebingen.de.

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.

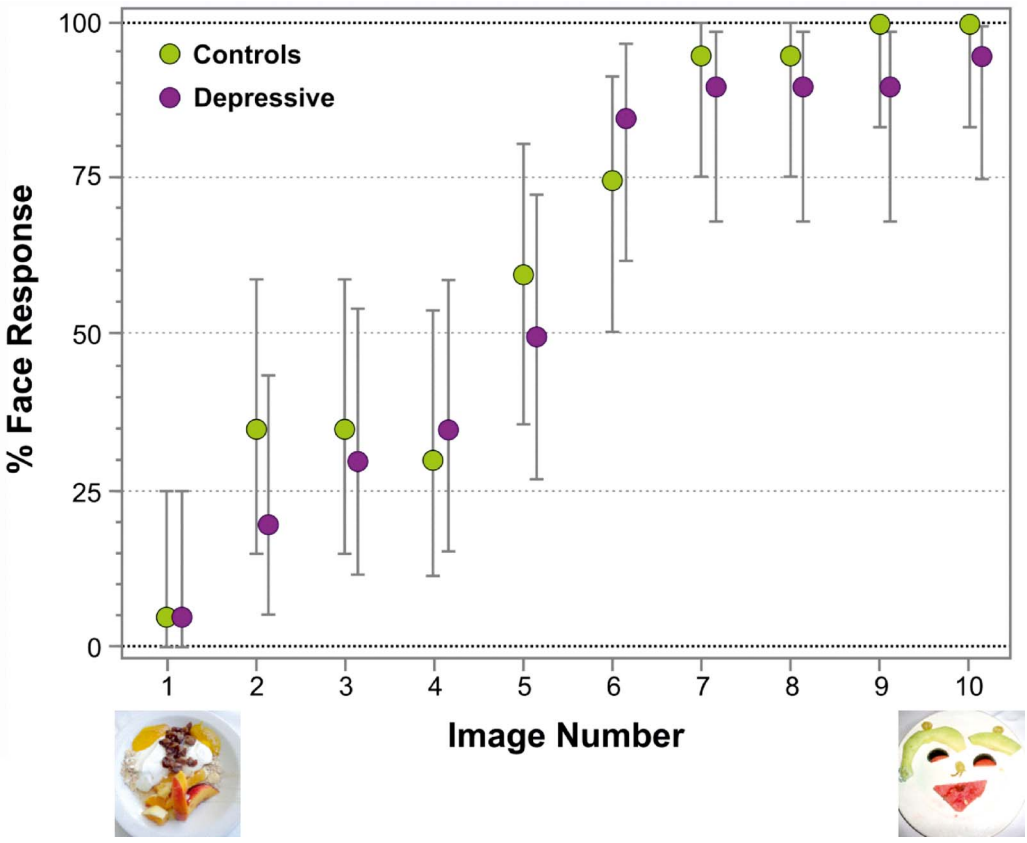

Figure 2. Percentage of face responses for each Face-n-Food image in patients with major depressive disorder, MDD (violet) and typically developing, TD, controls (green). The image number reflects its face resemblance (1, the least resembling a face, through 10, the most resembling a face images from 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

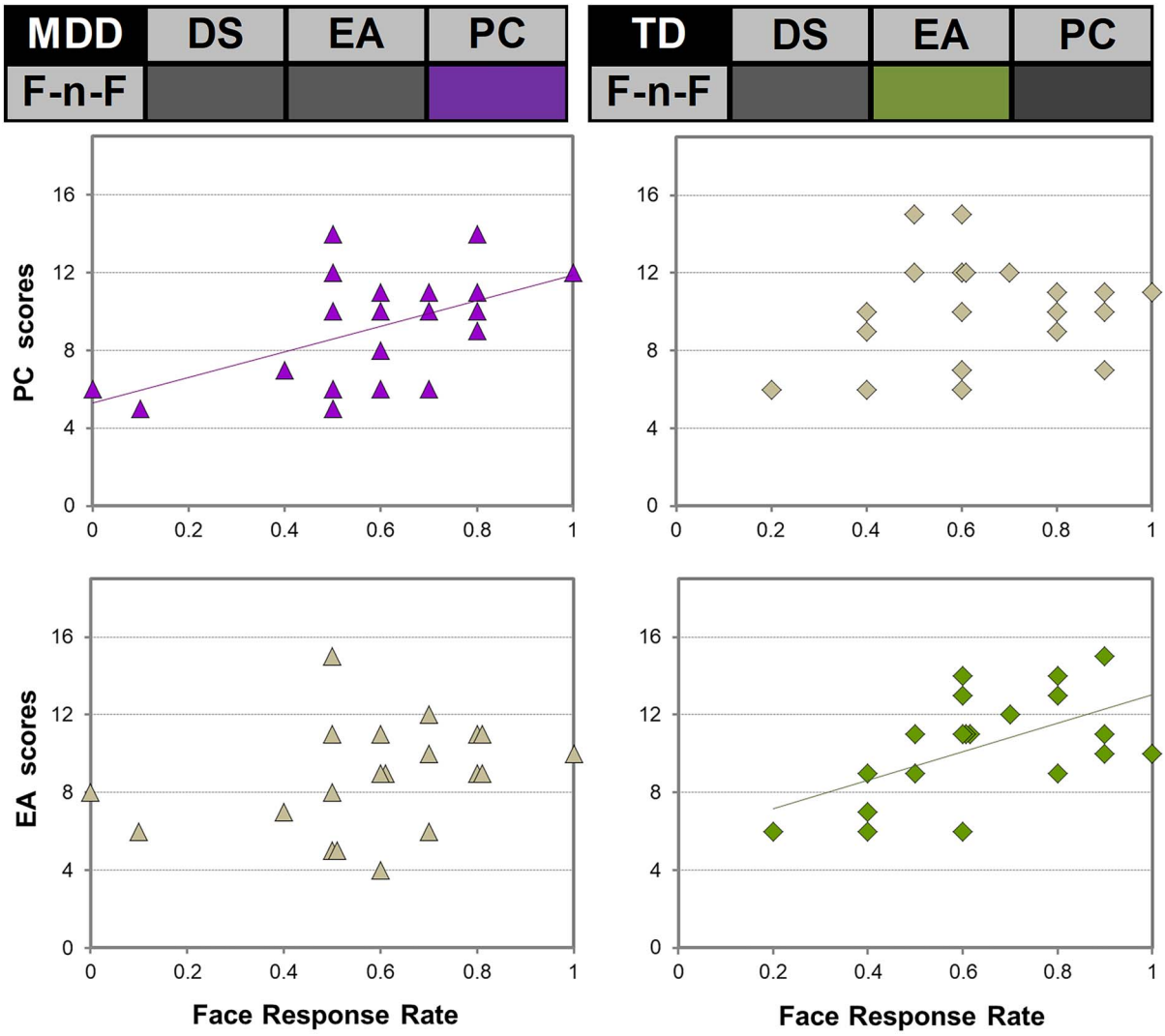

Figure 3. Relationship between the face response rate on the Face-n-Food task and scores on the digit span (DS), event arrangement (EA), and picture completion (PC) tests in MDD patients (left panel, triangles) and TD individuals (right panel, diamonds). In MDD, face response rate is positively linked 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

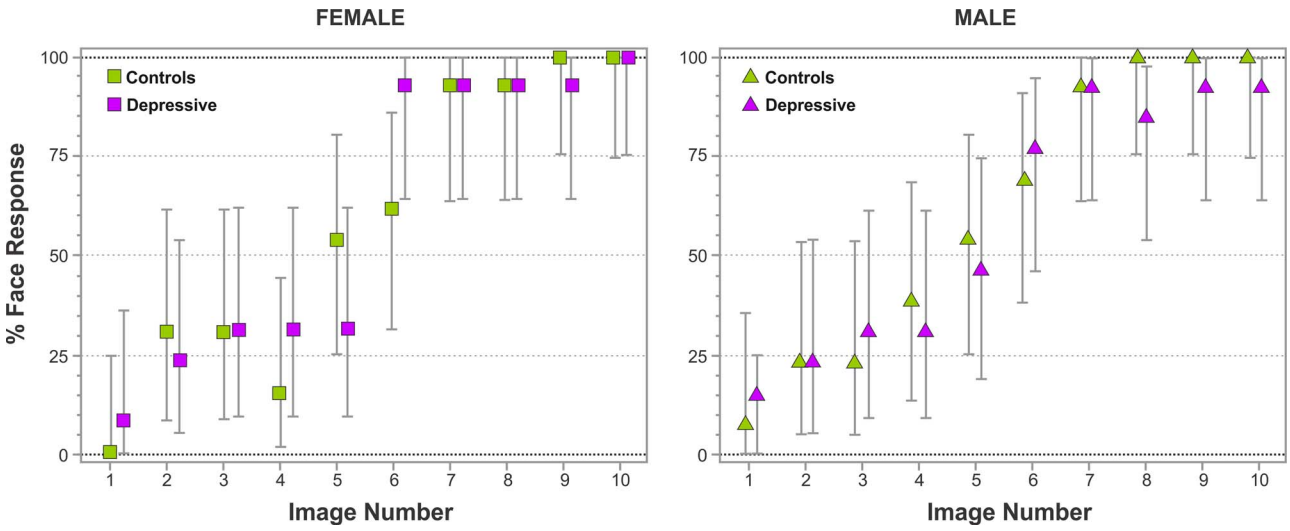

Figure 4. Percentage of face responses for each Face-n-Food image in female patients with MDD and controls (violet and green squares, respectively; left) and male MDD patients and controls (violet and green triangles, respectively; right). The image number reflects its face resemblance (1, the least 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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Supplementary Table 1

Comorbidity in MDD individuals

Patient code	Sex	Comorbidity
P01	F	Late-onset psychotic disorder due to use of hallucinogens (F16.7) Harmful use of tobacco (F17.1) Overeating associated with other psychological disturbances (F50.4)
P02	F	Histrionic personality disorder (F60.4)
P03	F	Panic disorder (F41.0) Post-traumatic stress disorder (F43.1) Histrionic personality disorder (F60.4)
P04	F	Harmful use of alcohol (F10.1) Obsessive-compulsive disorder (F42)
P05	F	Panic disorder (F41.0)
P10	F	Unspecified somatoform disorder (F45.9) Neurasthenia (F48.0)
P13	M	Social phobias (F40.1) Anxious personality disorder (F60.6)
P14	F	Mixed personality disorder (F61)
P16	F	Post-traumatic stress disorder (F43.1) Anxious personality disorder (F60.6) Pathological gambling (F63.0)
P17	M	Emotionally unstable personality disorder of borderline type (F60.3)
P18	M	Sedative, hypnotic or anxiolytic-related dependence (F13.2) Generalized anxiety disorder (F41.1) Anxious personality disorder (F60.6)
P19	M	Attention deficit hyperactivity disorder (F90.0)
P21	M	Mixed personality disorder (F61)
P22	M	Harmful use of sedatives or hypnotics (F13.1) Mixed obsessional thoughts and acts (F42.2)

No difference occurred between patients with and without comorbidity across all tasks administered in the study.

2.2 Neural circuits underpinning face tuning in male depression

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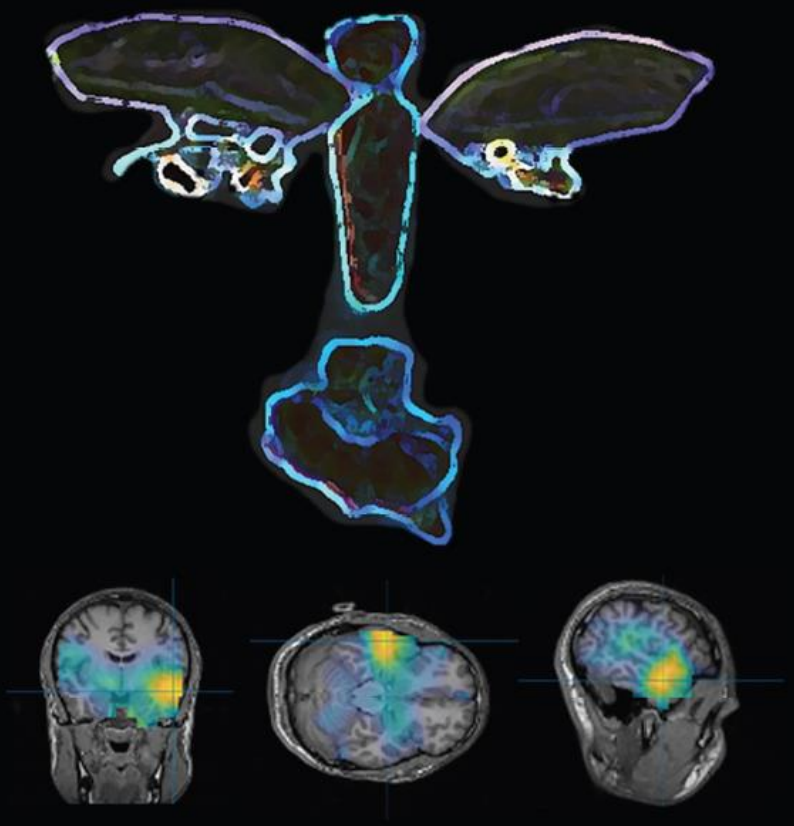

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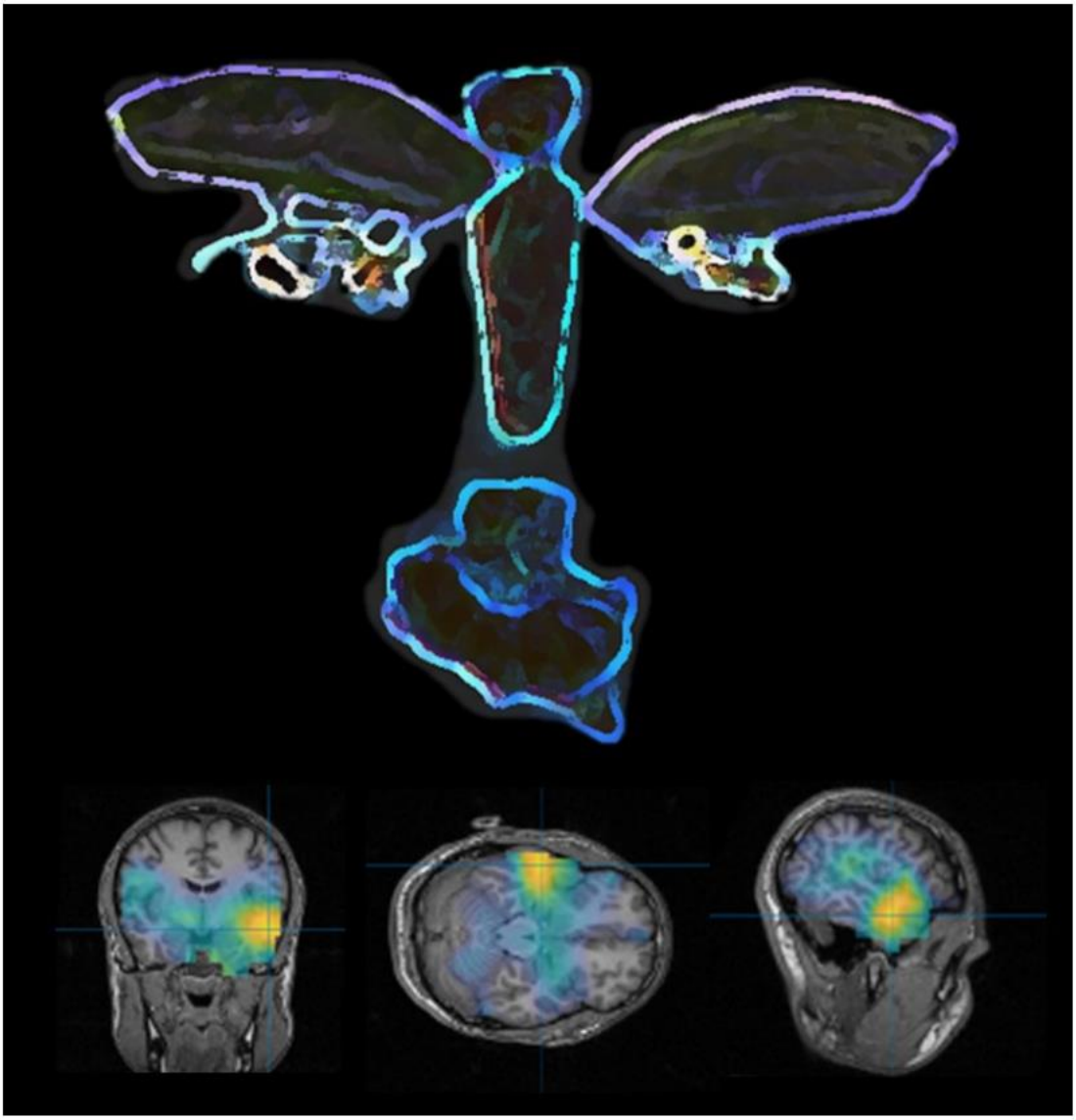

Cover Picture: As shown by magnetoencephalography (MEG), at early stages, face pareidolia images (arty representation) are rather similarly processed by the brain in patients with major depression disorder (MDD) and healthy controls. The primary difference occurs later over the left middle temporal cortex, a part of the social brain, engaged in feature integration and meaning retrieval. See Kubon et al. 2023. Neural circuits underpinning face tuning in male depression. Cereb Cortex 33(7): 3827-3839.

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Feature Article

Neural circuits underpinning face tuning in male depression

Julian Kubon[1], Valentina Romagnano[1], Alexander N. Sokolov[1], Andreas J. Fallgatter[1], Christoph Braun[2], Marina A. Pavlova[1,*]

[1]Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), Medical School and University Hospital, Eberhard Karls University of Tübingen, Calwerstr. 14, 72076 Tübingen, Germany,
[2]MEG Center, Medical School and University Hospital, Eberhard Karls University of Tübingen, Otfried Müller Str. 47, 72076 Tübingen, Germany
*Corresponding author: Prof. Marina A. Pavlova, Social Neuroscience Unit, Department of Psychiatry and Psychotherapy, Medical School, Eberhard Karls University of Tübingen, Calwerstr. 14, 72076 Tübingen, Germany. Email: marina.pavlova@uni-tuebingen.de

Reading bodies and faces is essential for efficient social interactions, though it may be thought-provoking for individuals with depression. Yet aberrations in the face sensitivity and underwriting neural circuits are not well understood, in particular, in male depression. Here, we use cutting-edge analyses of time course and dynamic topography of gamma oscillatory neuromagnetic cortical activity during administration of a task with Arcimboldo-like images. No difference in face tuning was found between individuals with depression and their neurotypical peers. Furthermore, this behavioral outcome nicely dovetails with magnetoencephalographic data: at early processing stages, the gamma oscillatory response to images resembling a face was rather similar in patients and controls. These bursts originated primarily from the right medioventral occipital cortex and lateral occipital cortex. At later processing stages, however, its topography altered remarkably in depression with profound engagement of the frontal circuits. Yet the primary difference in depressive individuals as compared with their neurotypical peers occurred over the left middle temporal cortices, a part of the social brain, engaged in feature integration and meaning retrieval. The outcome suggests compensatory recruitment of neural resources in male depression.

Key words: male depression; social cognition; non-face Arcimboldo-like images; magnetoencephalography (MEG); gamma oscillatory cortical activity.

Introduction

Major depressive disorder (MDD) emerged as menace to affected individuals and public health (Barnett 2019). Already in 2008, MDD had been estimated to become the leading cause of disease burden in 2030 (Mathers et al. 2008). According to the Global Burden of Disease Study, the prevalence of MDD in 2017 reached 163 million people (James et al. 2018). MDD is not only a problem of modern lifestyle or poverty, but deeply rooted among different social groups with high years lost due to disability (YLD) numbers across low-, middle-, and high-income countries (James et al. 2018; Malhi and Mann 2018). The latest coronavirus disease of 2019 (COVID-19) pandemic, multimorbidity, and late-life depression suggest heterogeneity in clinical presentation and management of MDD patients (Read et al. 2017; Alexopoulos 2019; Qiu et al. 2020). Despite a variety of treatment concepts for MDD, remission rates are low, recurrence rates remain high, and insights in underlying mechanisms are limited (Hyman 2014; Mora et al. 2018; Jha and Trivedi 2019).

"Being female" is listed among robust risk factors of MDD (Hammen 2018). Indeed, the prevalence rates of MDD differ between males and females, with females being about twice as often affected (Salk et al. 2017). Apart from a proposed biological susceptibility (i.e. hormonal causes and genetic background) and unequally distributed psychosocial factors (e.g. educational and socioeconomic status, and decisional control), cognitive factors contribute to female preponderance: rumination (a form of perseverative cognition that focuses on negative content) and co-rumination (revisiting problems and speculating about problems with focusing on negative feelings), neuroticism, and deficits in positive affectivity are considered to drive female MDD (Kuehner 2017).

Other factors impact male depression. Young boys frequently experience depression as a result of underlying neuropsychiatric disorder. This is often referred to as the early onset subtype of depressive symptoms (Douglas and Scott 2014). In the life course, male depression becomes an underdiagnosed and often untreated clinical entity (Seidler et al. 2016). MDD accounts for the highest suicide rate among all mental disorders (Bachmann 2018), and men are at particularly high risk. Characteristics of adult male depression are: (i) the distinct clinical phenotype with higher rates of externalizing symptoms (among which are substance misuse, irritability, anger, and risk-taking); (ii) the low rates of clinically diagnosed male depression along with pronounced high risk for suicide; (iii) social stigma, self-stigma, and traditional masculine gender norms, which run contrary to the

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need for professional help; and (iv) the need for new system-oriented treatment strategies (empowerment and self-management; Oliffe et al. 2019). This calls not only for tailored treatment concepts, but also for societal rethinking of male depression at large. For instance, the male "breadwinner" model is wide-spread in many countries with more traditional masculine gender norms and stereotypes, that may discourage men's help-seeking and affect the mode males experience and express depression (Seidler et al. 2016).

How affected individuals cope with demands of society, in particular, how effective they are in inferring drives, emotions, and desires of other people, becomes a key node in understanding male depression. Yet the relationship between MDD and social cognitive abilities is sparely explored. The most essential pillars of social cognition are body and face reading (de Gelder et al. 2010; Kret and de Gelder 2012; Pavlova 2012, 2017a, 2017b; Pelphrey et al. 2014; Di Giorgio et al. 2016, 2017; Pavlova et al. 2017a; Sokolov et al. 2018, 2020; Pavlova and Sokolov 2022a, 2022b). Social cognition deficits in MDD may be subtler than in other conditions (Wang et al. 2008; Bazin et al. 2009; Weightman et al. 2014). Most research focuses on processing of emotional information such as facial affect (Gollan et al. 2010; Seidel et al. 2010; Anderson et al. 2011; Csukly et al. 2011; Weightman et al. 2014), whereas the sensitivity to faces per se is under-investigated. Earlier, by applying a novel tool for examination of face tuning, a Face-n-Food task, we demonstrated intact face sensitivity in MDD (Kubon et al. 2021). On this task, a set of images containing food ingredients (such as fruits and vegetables, Fig. 1; Pavlova et al. 2015, 2016a, 2016b, 2017b, 2018a, 2018b, 2021; Rolf et al. 2020; Kubon et al. 2021) is presented. Similar to the portraits of a genius Italian painter Giuseppe Arcimboldo, the face-like non-face food compositions resemble faces. The main benefit of these images is that their single components do not trigger face processing. Despite the lack of difference in face tuning between MDD and typically developing (TD) individuals, the face sensitivity in MDD is linked in a different way to other social and cognitive abilities: Whereas face sensitivity in neurotypical individuals is associated with social cognitive abilities, in MDD, it is intimately tied with perceptual organization abilities. This suggests that altered neural circuits may be recruited by MDD individuals to reach a comparable behavioral outcome.

Visual processing of Face-n-Food images may be supported by gamma oscillatory activity that underlies perception of Gestalt. In addition to information processing in time domain and synchronization of neuronal activity, gamma oscillations (above 30 Hz; Buzsáki and Wang 2012) are linked to various perceptual and cognitive abilities such as working memory and selective attention (Sokolov et al. 1999, 2004; Fries et al. 2001; Tallon-Baudry 2009; Uhlhaas et al. 2011; Başar 2013; Herrmann et al. 2016; Kaiser et al. 2017; Miller et al. 2018; Stauch et al. 2021). Gamma oscillations underlie also processing of social signals such as faces, face-like images, body motion, and even social-like interaction between simple geometric shapes (Rodriguez et al. 1999; Pavlova et al. 2004, 2010; Dobel et al. 2011; Moratti et al. 2014; Müsch et al. 2017; Kajal et al. 2020; Yin et al. 2020; Grove et al. 2021). Modulation of oscillatory activity in the gamma band during face processing is reported to be associated with anxiety (Schneider et al. 2018). Recent work illuminates the relevance of gamma oscillations in depression: Patients show altered gamma activity during cognitive, emotional, and attention tasks, and these alterations may be considered a potential biomarker of MDD (Fitzgerald and Watson 2018).

The present work was aimed at clarification of the issue of whether neural networks underwriting face sensitivity are altered in MDD. To this end, we used magnetoencephalography (MEG), a non-invasive brain imaging technique providing for high temporal resolution, which is of great advantage for uncovering of undergoing brain activity and comparison of patients with healthy individuals (Pavlova 2017a, 2017b). We analyzed gamma oscillatory activity during visual processing of Face-n-Food images with upright display orientation and with display inversion that severely impedes face impression, in particular, in males (Pavlova et al 2020) (Fig. 1). For better understanding social cognition in male MDD, we set a focus on this patient population.

Method

Participants

Twenty-five male patients with MDD were enrolled in MEG recording. Due to excessive artifacts in MEG traces, 3 of them were excluded from data processing, so that 22 patients aged 37.5 ± 8.8 years (mean, standard deviation; age range from 22 to 50) entered final analysis. TD male individuals matched person-by-person for socioeconomic and educational status were recruited from the local community. They were aged 36.8 ± 8.6 years (age range from 22 to 49). No difference in age occurred between MDD patients and controls ($t(42) = 0.277$, $P = 0.783$, 2-tailed, n.s.). The sample size was determined by demands of statistical data processing, and was calculated a priori taking into account possible dropouts. Psychotic form of MDD or hypomanic/manic phases as well as a history of neurological disorders (such as epilepsy) served as exclusion criteria. All patients were in a post-acute phase. Most patients (20) were diagnosed to be recurrently depressive (ICD-10; F33): 9 patients with F33.1 (moderate form); and 11 patients with F33.2 (severe form without psychotic symptoms). Two patients had a diagnosis of MDD single episode (ICD-10; F32): 1 patient with F32.1 (moderate form); and 1 patient with F32.2 (severe form without psychotic symptoms). The majority of patients reported consumption of drugs in the past (cannabinoids [9 patients], amphetamines [5], cocaine [3], heroine [1]) and other psychotropic substances (angel trumpet and nutmeg [1], alcohol [16], and/or nicotine [10]). Among comorbid disorders were

Fig. 1. "Portrait of the man made of fruit" (leftmost), "The Gardener" (middle), and "The Cook" (right; https://commons.wikimedia.org/wiki/Giuseppe_Arcimboldo; public domain) by Giuseppe Arcimboldo. Rightmost: One of the Face-n-Food images (from Pavlova et al. 2015, the Creative Commons Attribution [CC BY] license). The top row represents the images inverted 180° in the image plane.

mainly personality disorders [mixed personality disorder (F61), narcissistic personality disorder (F60.8), anxious personality disorder (F60.6), borderline personality disorder (F60.31), emotionally unstable personality disorder (F60.3), anankastic personality disorder (F60.5) with narcissistic and emotionally unstable features (F61)], phobias [social phobia (F40.1), paruresis (F40.2), and emetophobia (F40.2)], and game addictions [video game addiction (F63.8), pathological gambling (F63.0)]. Patients were recruited from the Department of Psychiatry and Psychotherapy, University Hospital, Eberhard Karls University of Tübingen. As a part of treatment regimen, all patients received antidepressants (e.g. SSRI/SNRI, tricyclic antidepressants, and mirtazapine) and/or antipsychotics and/or sedatives.

Participants had either normal or corrected by MEG-conform refractive compensation vision. 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. All participants gave informed written consent.

Experimental design and procedure

The Face-n-Food images (Pavlova et al. 2015, 2016a, 2016b, 2017b, 2018a, 2018b, 2021; Rolf et al. 2020; Kubon et al. 2021) to a different degree resembling a face were used. The stimuli were presented either with canonical upright orientation or inverted (rotated 180° in the image plane; Fig. 1). During each MEG recording session, participants were administered a set of 192 stimuli (12 images × 2 types [original/mirror image] × 2 display orientations [upright/inverted] × 4 repetitions). No more than 4 images with the same orientation appeared consecutively; this way, a possible adaptation of the visual system to display orientation was prevented. On each trial in a 2-AFC (2-alternative forced-choice) task, participants had to indicate whether they had seen a face. They were instructed that there were no correct or incorrect responses on the task and they had to rely upon their own visual impression solely. Participants were asked to respond (to press respective keys for face impression and non-face impression, accordingly) only after stimulus offset to avoid a possible influence of motor responses on the recorded MEG traces. If participants failed to respond, the next trial automatically started after an inter-stimulus interval randomly varying between 3,000 to 5,000 ms. The stimuli were presented in a pseudo-randomized order with a stimulus duration of 1,200 ms. Each stimulus subtended a visual angle of 10.2° (with an image size on the screen 12.5 × 12.5 cm at an observation distance of 70 cm). Prior to each image, a small fixation cross was presented in the center of the screen for 2,000 ms. The images were presented via a PROPixx 1,440 Hz DLP LED Projector (VPixx Technologies Inc., Saint-Bruno, QC, Canada). The visual task was built with Presentation software scripts (Version 20.3, Neurobehavioral Systems, Inc., Albany, CA, United

States). For each participant, the recording session lasted for ~12–17 min.

MEG recording and analysis

MEG measurement

Recording was conducted with a whole-head MEG system containing 275 axial magnetic gradiometers (VSM MedTech Inc., Coquitlam, BC, Canada). This system is operated in an electromagnetically shielded chamber (Vacuum Schmelze GmbH & Co. KG, Hanau, Germany) at the MEG Center, University Hospital of Tübingen. Signals were recorded at a rate of 1,171.88 Hz with a 293-Hz antialiasing low-pass filter. During the whole measurement, head movement in relation to the magnetic field sensors was registered with 3 localization coils placed at the nasion, and left and right periauricular points. Participants were instructed to blink only between trials, if necessary. MEG data analysis was performed with in-house MATLAB scripts (MATLAB 2020a; The MathWorks Inc., Natick, MA, United States) and the Fieldtrip toolbox (Version fieldtrip-20201229; Oostenveld et al. 2011).

Data preprocessing

Individual continuously recorded MEG data were segmented into 192 trials and high-pass filtered at 1 Hz. In order to exclude filter artifacts at the beginning and end of the segments, they were defined generously 1.5 s before and 1.5 s after stimulus onset with full coverage of the 1.2 s stimulus presentation time. For each trial, the interval between 500 and 300 ms pre-stimulus during which the fixation cross was presented served as baseline to which the subsequent activation was compared. Data were inspected visually and trials with large variance across channels ($>2 \times 10^{-25}$ T^2/Hz) were removed. In 13 datasets, artifact-contaminated channels characterized by large variance across trials, were discarded (no more than 12 per subject). Channels removed during visual rejection were interpolated for sensor-level analyses. Afterwards, data were downsampled to 250 Hz. For further artifact detection, independent component analysis (ICA) was performed by administering the infomax ICA algorithm (Bell and Sejnowski 1995; Amari et al. 1997). After decomposing the data into 272 components, topography and waveform of all components were plotted. The first 80 components were manually inspected for ocular (eye blinks and eye movements), muscular, and cardiac artifacts. Artifact-containing components and trials were discarded and a cleaned MEG signal was computed. After data preprocessing, the dataset included in total 3,904 trials of 22 patients and 3,840 trials of 22 matched control participants with no difference between the groups (Mann–Whitney test, $U = 196.5$, $P = 0.285$, 2-tailed, n.s.).

Categorization of data and time-frequency analysis

The preprocessed and cleaned trials for each participant were classified by Display Orientation (upright/inverted) and Participants' Response (face/non-face). For reaching a maximal contrast between face and non-face impression, we compared trials with upright stimulus presentation, for which participants indicated face impression (face responses), and trials with inverted presentation, for which participants indicated a lack of face impression (non-face responses). For time-frequency analysis (time-frequency representation, TFR), such contrast was calculated for each participant. Due to the unequal number of trials for face responses with upright orientation and non-face responses with display inversion, the condition (face responses/non-face responses) with the least number of trials (N_{min}) was determined and compared with randomly selected N_{min} trials of the other condition. Therefore, across participants and conditions, 38.77 ± 15.11 trials in MDD and 41.59 ± 12.68 trials in TD (with no group difference $t(42) = 0.670$; $P = 0.506$, 2-tailed, n.s.) entered time-frequency analysis. Individual TFRs for each condition (face/non-face) were computed in a frequency range from 2 to 98 Hz by administering Hanning tapers with a fixed time window of 500 ms, 2-Hz frequency resolution, and 50-ms sliding windows starting from 1.25 s pre-stimulus to 1.25 s post-stimulus onset (Percival and Walden 1993; Mitra and Pesaran 1999). Finally, the grand average of TFR data was obtained separately for controls and MDD patients.

Statistical inference

Statistical analysis of TFR data was performed by means of cluster-based nonparametric permutation tests. These clusters contained spatio-temporo-spectral, i.e. 3-dimensional data. We chose 2-tailed cluster-based test statistics with a cluster-alpha of 0.05 and a required minimum cluster size of 2 neighboring channels. This method has proven sufficient to correct for family-wise error (FWE) rates for multiple comparisons (Maris and Oostenveld 2007). The channel-time-frequency triplets with a *t*-value exceeding a threshold (as determined by the cluster-alpha) were then clustered based on their spatial, spectral, and temporal adjacency. Subsequently, the maximum sum of *t*-values was used to construct the permutation-based random distribution. The significance level was calculated with the Monte Carlo method based on a set of 1,000 permutations. Statistical testing was performed on relative power changes with respect to baseline (500–300 ms pre-stimulus). Cluster search was limited to the time window of stimulus presentation (0–1.2 s) to infer the effects of condition (face/no face) and group (patients/controls). To obtain a finer frequency resolution, statistical analyses were performed independently for individual frequencies in the gamma range of 30–45 Hz in steps of 5 Hz.

Source reconstruction

Source localization based on time windows and frequency ranges of the significant clusters was performed using a beamformer approach implemented in Fieldtrip.

To obtain cross-spectral density data, TFR analysis was performed using discrete prolate spheroidal sequence (DPSS) tapers. The spectrum was calculated for the mean of the significant clusters' frequency range with a time window of 500 ms sliding forward in steps of 50 ms from 1.25 s pre- to 1.25 s post-stimulus. For further source reconstruction, a canonical MNI (Montreal Neurological Institute) template specified in a coordinate system defined by the fiducials nasion, left and right periauricular points was segmented. A single shell volume conduction model was derived from the brain scan (Nolte 2003). As a 3-dimensional source model, a regularly spaced grid was established with 1-cm spacing. Source analysis was based on the dynamical imaging of coherent sources (DICS) approach (Gross et al. 2001). Common spatial filters for both conditions were derived from the cross-spectral density (CSD) matrix of the TFR data and leadfield matrix. Applying the spatial common filters resulted in TFRs for each condition and grid point, reflecting the time course of the spectral source strength.

Picture completion test

Similar to our previous study in MDD (Kubon et al. 2021), a picture completion (PC) task was administered to both MDD and TD participants outside of MEG dewar. The task is a part of the Wechsler-Intelligenztest für Erwachsene (WIE), a well-established neuropsychological assessment battery, Wechsler Adult Intelligence Scale (WAIS-III), adapted to the German population (von Aster et al. 2006). On this task, near-to-complete pictures (with a missing piece) are presented to participants one by one. The test assesses the participant's capabilities for visual perceptual organization, which are required for identification of a missing part within the presented object or scene.

Beck Depression Inventory-II

The Beck Depression Inventory-II (BDI-II) was applied for quantification of MDD severity. Investigating standard depressive features (e.g. low mood, loss of self-confidence, sleeplessness, and appetite changes), it is a wide-spread, reliable, and valid diagnostic tool in clinical practice (Hautzinger et al. 2009; Wang and Gorenstein 2013). As the study was conducted during the COVID-19 pandemic, which potentially had an influence on mental well-being, the BDI-II was also administered to TD participants. The BDI score was 26.09 ± 10.01 in the group of MDD patients and 2.73 ± 2.60 (Mdn, 1.50; 95% confidence interval, CI, 1.57–3.88) among TD individuals. The group difference was highly significant (Mann–Whitney test, $U = 2.5$, $P < 0.001$, 2-tailed). None of TD participants reached clinically significant BDI scores (BDI ≤ 9 for all TD controls).

The whole examination (instructions, paper work, MEG preparation and recording, PC and BDI-II testing) lasted ~90–110 min for each participant.

Normality of data distributions

By applying Shapiro–Wilk test, all data sets were routinely checked for normality of distribution. For normally distributed data, we further used parametric statistics, including analyses of variance, ANOVA. In addition to means and SDs, Mdns and 95% CIs are reported for non-normally distributed data with subsequent use of non-parametric statistical tests. Statistical testing of patient characteristics and behavioral data was performed with SPSS (Version 26, IBM, Armonk, NY, United States) and JMP (Version 16, SAS Institute, Cary, NC, United States) packages.

Results

Behavioral data analysis

Individual data on face response rates were submitted to a 2-way mixed-model ANOVA with a within-subject factor Display Orientation (upright/inverted) and a between-subject factor Group (MDD/TD). The main effect of Display Orientation was significant ($F(1,42) = 50.78$, $P < 0.001$, effect size, eta-squared, $\eta^2 = 0.547$) with higher face response rates for upright presentation, whereas neither the main effect of Group ($F(1,42) = 1.75$, $P = 0.193$, n.s.), nor an interaction between these factors ($F(1,42) = 0.07$, $P = 0.789$, n.s.) were significant. Post-hoc analysis (by using 2-tailed Tukey honestly significant differences (HSD) tests corrected for multiplicity) indicated that (i) no significant differences in face responses occurred between the MDD and TD groups for both upright (MDD: 0.686 ± 0.150; TD: 0.636 ± 0.129; $t(42) = 1.13$, $P = 0.676$, n.s.) and inverted display orientation (MDD: 0.453 ± 0.264; TD: 0.420 ± 0.205; $t(42) = 0.74$, $P = 0.879$, n.s.); and (ii) display inversion substantially impeded face recognition in MDD ($t(21) = 5.23$, $P < 0.001$, effect size, Cohen's $d = 1.59$) as well as in TD individuals ($t(21) = 4.85$, $P < 0.001$, effect size, $d = 1.57$).

In MDD patients, there was no correlation between severity of depressive symptoms as measured by the BDI-II and face response rates either with upright or inverted display presentation (Pearson product–moment correlation, $r(20) = -0.006$, $P = 0.977$ for upright, $r(20) = 0.040$, $P = 0.859$ for inverted orientation, 2-tailed). Furthermore, there was a significant correlation between face response rate with upright orientation and scores on the PC task ($r(20) = 0.423$, $P = 0.05$). In contrast, no significant correlation between these 2 variables occurred in TD controls (Spearman rank correlation, *rho*, $\rho(20) = 0.125$, $P = 0.580$, n.s.). This is in accord with our earlier study in MDD (Kubon et al. 2021) conducted with a different task using Face-n-Food images and a separate patient group.

MEG analysis

Increases in gamma oscillations relative to baseline

In controls, significant stimulus-specific (i.e. present for face impressions, but absent for non-face impressions) increases in early (from 0 to 250 ms after stimulus onset, $P = 0.024$, corrected throughout) gamma oscillatory

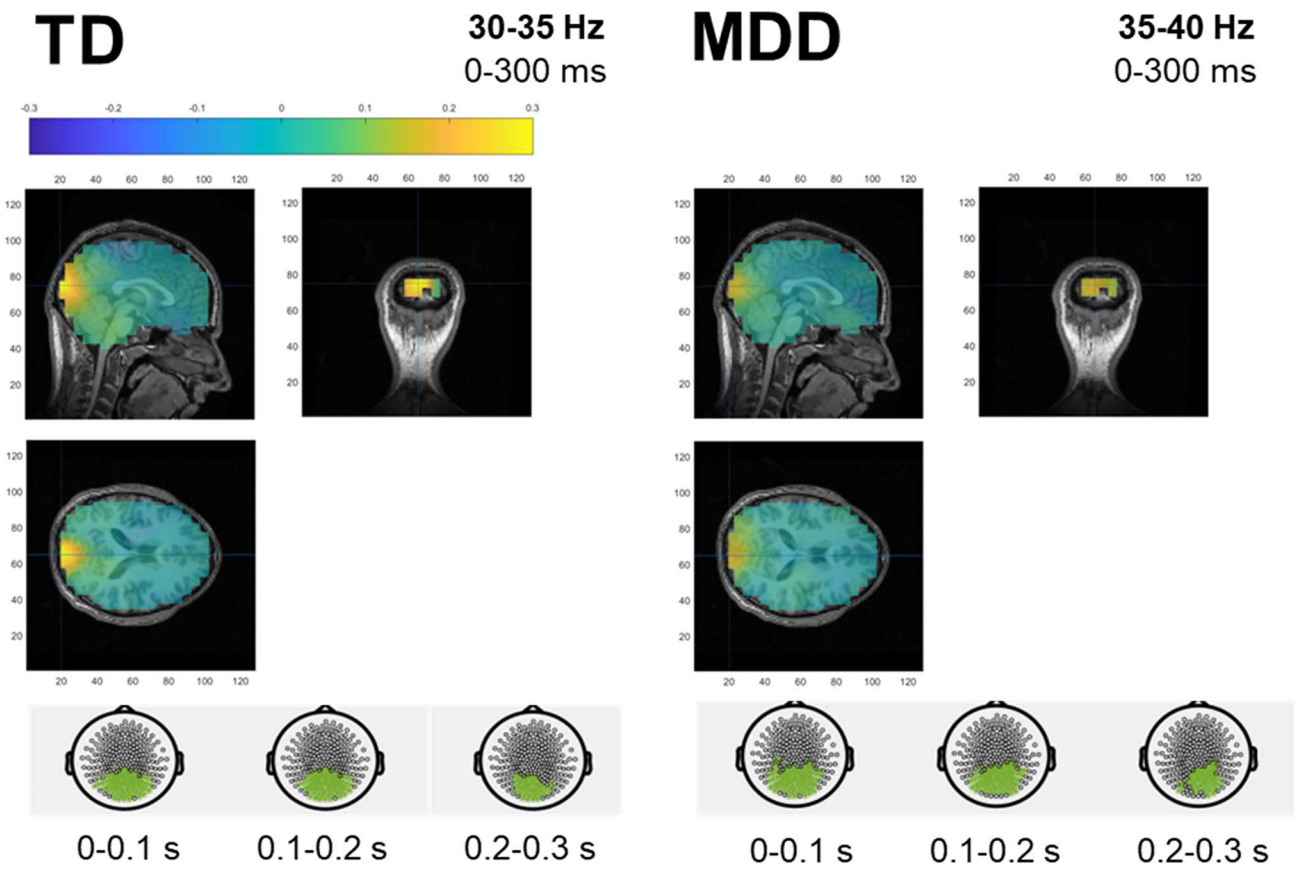

Fig. 2. Source reconstruction and cluster visualization for face responses versus baseline. Gamma oscillatory activity during early processing (0–300 ms) originated from the right MVOC and LOC in the frequency range of 30–35 Hz in TD (left panel) and 35–40 Hz in MDD individuals (right panel). Source plots represent positive peaks relative to baseline in yellow, negative in blue. Channels constituting the significant clusters are highlighted in green in steps of 100 ms (bottom).

activity occurred in the frequency range of 30–35 Hz. For non-face responses, no increases were observed during the whole stimulus duration. Source localization analysis indicated that these increases originated from the brain areas heavily involved in visual face processing with the maximum in the medioventral occipital cortex (MVOC) and lateral occipital cortex (LOC, Fig. 2) of the right hemisphere.

Such stimulus-specific activity was absent in patients: No significant clusters of increased oscillatory activity were found in this frequency range for both face and non-face responses. Instead, in patients, significant stimulus-specific differences in early activity were found in the higher frequency range of 35–40 Hz during the first 300 ms from the stimulus onset ($P = 0.019$). Notably, source localization analysis indicated that topographically, this cluster appeared to be of similar origin as the cluster in controls found at a lower frequency (30–35 Hz; Fig. 2). For the range of 30–35 Hz, in MDD patients, no significant peaks of activity were found for face responses at later processing stages. Significant increases were also absent for non-face responses over the whole stimulus duration.

In the frequency range of 35–40 Hz, in controls, clusters of increased oscillatory activity were found during the whole stimulus presentation (1,200 ms; $P = 0.004$). However, early oscillatory activity peaked also for non-face responses (0–300 ms; $P = 0.035$), and, therefore, these early increases were not stimulus-specific. Late stimulus-specific activity (700–1,000 ms) for face responses originated from the superior frontal gyrus (SFG) and inferior frontal gyrus (IFG) of the left hemisphere.

Face versus non-face contrast

In controls, within-group analysis pointed to several significant clusters of gamma oscillations in response to face impressions as compared with non-face impressions in late activity only (30–35 Hz: 0.7–1.2 s, $P = 0.01$; 35–40 Hz: 0.55–1.2 s, $P = 0.01$; 40–45 Hz: 0.7–1.2 s, $P = 0.047$). The source localization analysis revealed increases in gamma oscillations in the left postcentral gyrus at frequencies 30–35 Hz, right precentral gyrus at 35–40 Hz, and right inferior parietal lobule at 40–45 Hz (Fig. 3).

In MDD patients, significant clusters were also found in late oscillatory gamma activity at 30–35 Hz (0.7–1.2 s from stimulus onset, $P = 0.028$) and 35–40 Hz (0.9–1.2 s, $P = 0.027$). The source localization analysis conducted in these time windows pointed to the left middle frontal

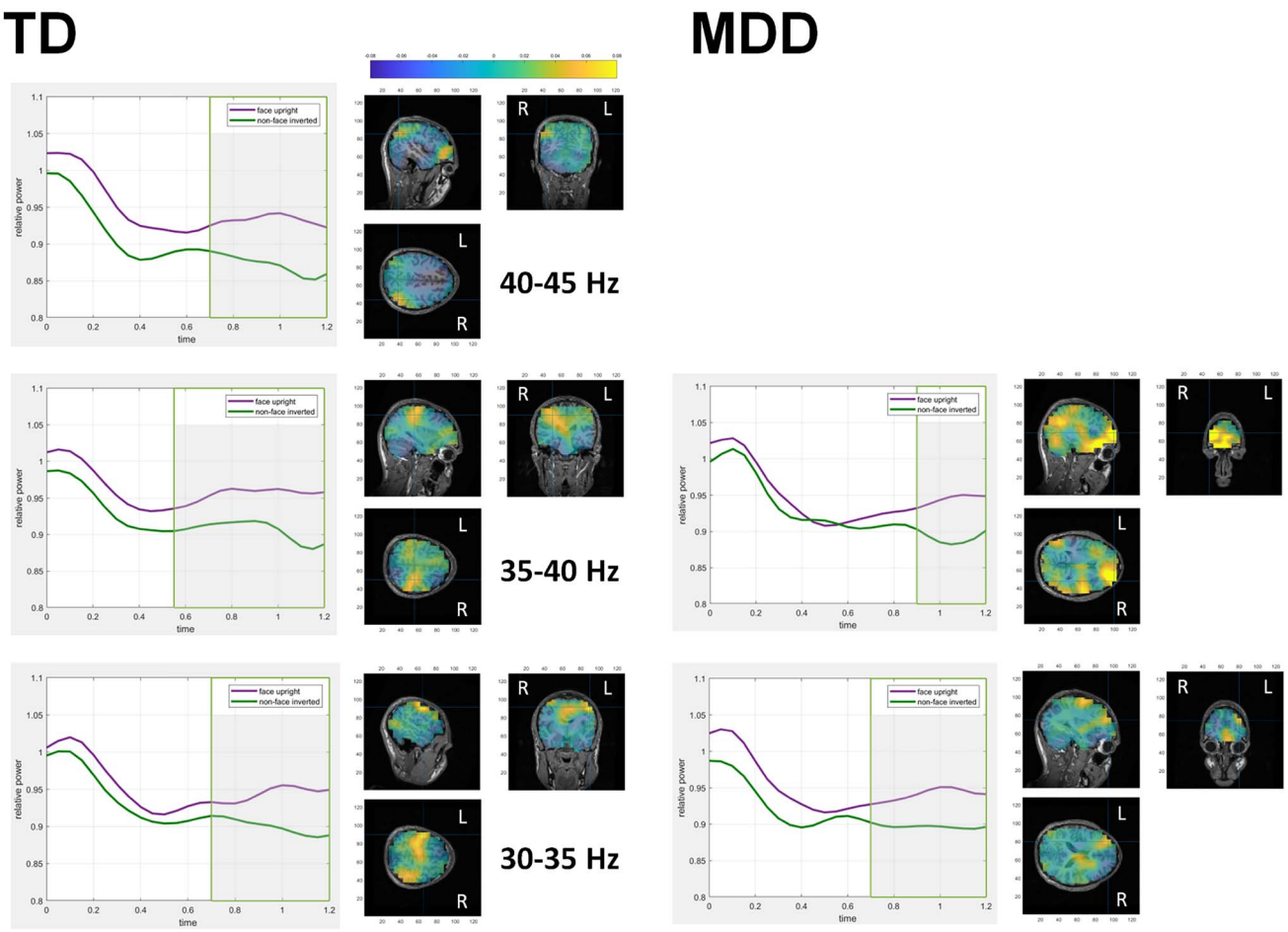

Fig. 3. Contrast of gamma oscillatory activity between face versus non-face responses. Curves represent the time course of relative power differences (baseline corrected) plotted for face (violet) and non-face (green) conditions over the stimulus duration with stimulus onset at 0 s. Gray shaded boxes indicate time windows of significant clusters of increased gamma oscillations. In controls, source plots show positive power differences between conditions in the left postcentral gyrus at frequencies 30–35 Hz (bottom and left), right precentral gyrus at 35–40 Hz (middle and left), and right inferior parietal lobule at 40–45 Hz (top and left). In patients, these differences originated from the left middle frontal gyrus at frequencies 30–35 Hz (bottom and right), and the right middle frontal gyrus at 35–40 Hz (middle and right). Positive differences are indicated by yellow, negative by blue color.

gyrus at a frequency range of 30–35 Hz and the right middle frontal gyrus at 35–40 Hz.

Notably, significant clusters of oscillatory gamma activity at frequencies 30–35 Hz in the late response (0.7–1.2 s) were of different topography in controls and patients (Fig. 3): while peaks in controls occurred primarily over the left postcentral gyrus, in patients they were localized more anterior, over the left middle frontal gyrus.

Between-group contrast

When contrasting oscillatory activity for face responses between controls and patients, we found one significant cluster at early latencies (0–300 ms, $P = 0.023$) in the frequency range of 35–40 Hz with a maximum activation in the left middle temporal gyrus, and one cluster at later latencies (600–900 ms, $P = 0.026$) in the frequency range of 40–45 Hz with rather comparable topography (Fig. 4).

Discussion

This work was aimed at investigation of brain mechanisms underlying the face sensitivity in male depression. With this purpose in mind, the recently developed Face-n-Food paradigm (Pavlova et al. 2015, 2016a, 2016b, 2017b, 2018a, 2018b, 2021; Rolf et al. 2020; Kubon et al. 2021) had been used during recording of neuromagnetic cortical activity. The outcome indicates: (i) At early stages of face processing, in both MDD and neurotypical individuals, stimulus-specific clusters of increased oscillatory gamma activity of similar topography originate primarily from the right MVOC and LOC. These boosts occur in the frequency range of 30–35 Hz in controls, whereas at slightly higher frequencies of 35–40 Hz in MDD patients. (ii) At later processing stages, clusters of increased oscillatory gamma response to face-like images are of different topography in MDD patients and TD controls. And, (iii) Gamma oscillations (35–45 Hz) in response to non-face Arcimboldo-like images are stronger in controls as compared with MDD patients over the left temporal cortices during the first 300 ms from the stimulus onset and from 600 to 900 ms, with a maximum in the left middle temporal gyrus, a part of the social brain, engaged in feature integration and meaning retrieval. In general, this outcome dovetails well with our earlier behavioral data (obtained in the

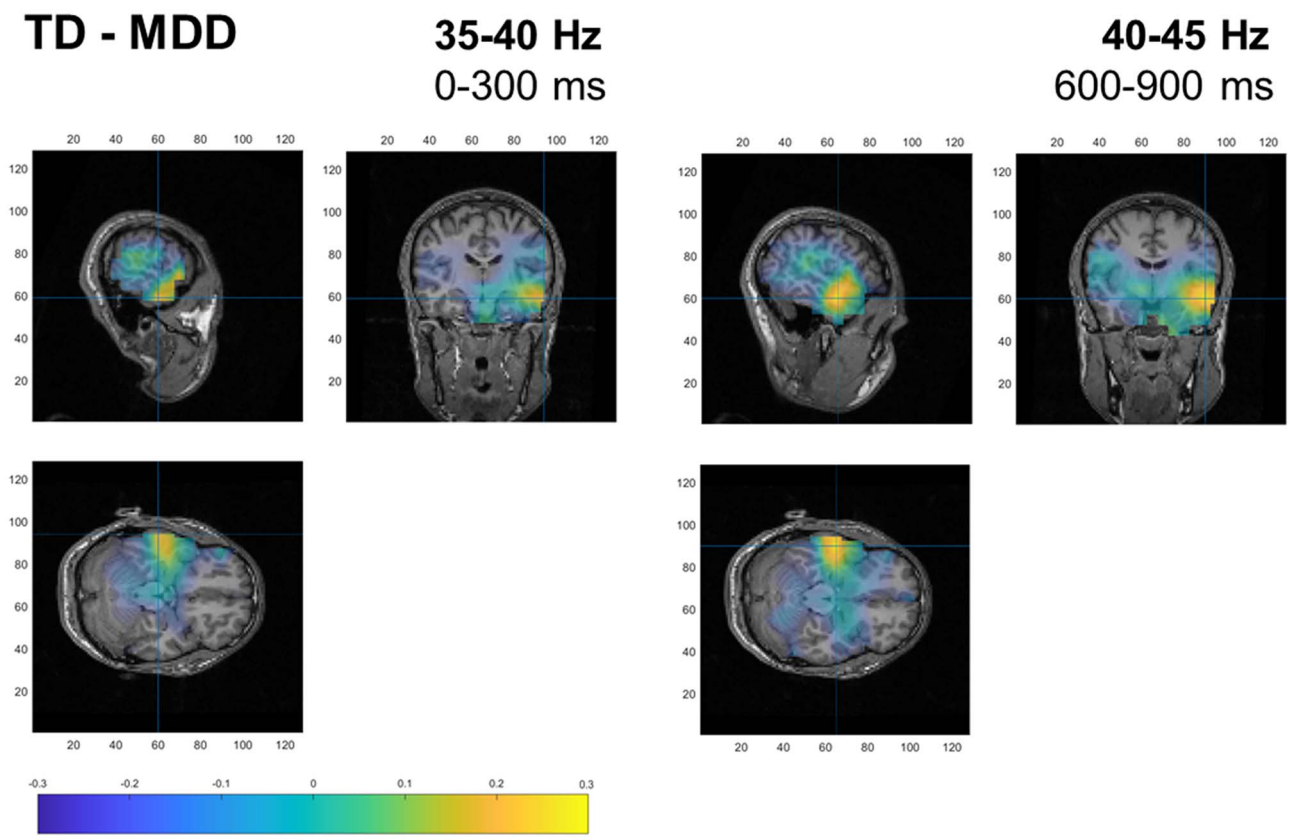

Fig. 4. Source reconstruction of contrast in gamma oscillatory activity for face responses between controls and patients. For both early (0–300 ms, 35–40 Hz, left) and late latencies (600–900 ms, 40–45 Hz, right), group differences arose in the left middle temporal gyrus. Positive differences are indicated by yellow, negative by blue colors.

other sample of MDD patients) demonstrating intact face tuning in MDD, but apparently distinct underlying strategies involved (Kubon et al. 2021).

Face processing in MDD

In clinical context, pathophysiology, diagnosis, treatment, and remediation of MDD are all directed towards integration of biological, psychological, and social factors constituting the "biopsychosocial model" of depression (Schotte et al. 2006; Papadimitriou 2017). Yet the origins of aberrant social functioning in MDD are still a matter of debate. Whereas some work points to deficits and biases in social cognitive abilities such as theory of mind, body language reading, and recognition of facial affect (Surguladze et al. 2004; Zobel et al. 2010; Cao et al. 2013; Loi et al. 2013; Kaletsch et al. 2014), other studies report rather subtle or reversible deficits (Bazin et al. 2009; Gollan et al. 2010; Suslow et al. 2010). As proposed earlier, MDD individuals may be particularly sensitive to social signals before the disease onset: Individuals with high sensitivity (or even with over-sensitivity) to social signals in combination with low psychological defense are more likely to become depressive (Kubon et al. 2021). Strictly speaking, MDD individuals may be competent in perceiving and understanding of others, but use maladaptive strategies in dealing with social agents as well as in overcoming challenging situations indicated by these signals. MDD patients can see what others see and feel, but they do not possess efficient enough strategies and capacities for coping with this sensory information (Csukly et al. 2011; Weightman et al. 2014).

In line with these assumptions, the outcome of the present work indicates rather similar face processing with no differences between MDD patients and TD controls in face responsiveness at behavioral level as well as in the time course and topography of gamma oscillatory cortical activity at early processing stages. The lack of difference in face response rate between MDD patients and TD controls agrees well with our earlier findings in an independent MDD patient group: By using non-face face-like Face-n-Food images in ascending order (i.e. presenting images from the least to most face resembling), we found comparable face thresholds in MDD patients and matched neurotypical individuals (Kubon et al. 2021).

Present MEG analysis shows that both MDD patients and TD controls exhibit marked boosts of early gamma oscillatory activity originating primarily from the right MVOC and LOC. Yet, there was a slight difference in the range of oscillations: whereas TD controls showed a stimulus-specific boost in the range of 30–35 Hz, in MDD patients, peaks occurred at higher frequencies of 35–40 Hz. During processing of sensory stimuli, brain oscillations in the gamma band are thought to be associated with increased neuronal action potential

generation (Fries et al. 2001; Kim et al. 2016; Fitzgerald and Watson 2018) and in such conditions as depression, with GABA(A) receptor regulation (Buzsáki and Wang 2012). As oscillation frequency is inversely related to time (i.e. oscillation period), higher gamma frequency reflects more swift neuronal processing in the brain while lower frequency, less swift processing. This leads to the expectations that more swift neuronal processing in MDD individuals underlies the higher face sensitivity in this patient population, and helps to compensate for possible deficient capacities in other domains such as attention capacity or decision-making. However, this consideration may be irrelevant for our findings, since the difference between TD and MDD individuals in oscillation range at early stages of face processing is not substantial.

Face tuning and underlying brain networks

In accord with our previous behavioral study performed with an independent group of MDD patients and a different paradigm (Kubon et al. 2021), the findings indicate that the face tuning in MDD and TD individuals differently relates to the scores on 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 this association is absent. Earlier data also indicate that in TD individuals, face response rate is related to social cognitive abilities as assessed by the event arrangement task, whereas in MDD this link is absent (Kubon et al. 2021). These considerations lead to an assumption that although MDD and TD individuals do not differ in performance on the Face-n-Food task, this outcome may be achieved by engagement of additional neural resources or recruiting diverse networks.

Indeed, the present findings show that although at early processing stages, the gamma oscillatory MEG response to non-face face-like images in MDD and TD individuals is rather similar in terms of topography and timing, its topography is remarkably different at later stages. In TD controls, gamma oscillations underlying face impressions as compared with non-face responses peak over the left postcentral gyrus at frequencies of 30–35 Hz from 0.7 to 1.2 s from the stimulus onset, the right precentral gyrus at 35–40 Hz from 0.55 to 1.2 s, and the right inferior parietal lobule at 40–45 Hz from 0.7 to 1.2 s. In MDD individuals, however, gamma activity peaks over the left middle frontal gyrus at frequencies of 30–35 Hz (0.7–1.2 s from stimulus onset), and the right middle frontal gyrus at 35–40 Hz (0.9–1.2 s). In general, at later processing stages, the parietal and central cortical areas are activated in TD individuals, whereas in MDD patients, (pre-)frontal regions are heavily involved. Frontal cortical areas are well-known to play a key role in MDD. Hyperactivity of the ventral paralimbic regions as well as hypoactivity of the frontal regions, and abnormalities of the prefrontal cortex in communication with striatal and subcortical structures point to deficient regulatory functions of the brain in MDD (Mayberg 1997; Hamilton et al. 2012; Graham et al. 2013). Affected individuals show aberrant functional connectivity in the default mode network (DMN), hyperactivity of the ventromedial PFC (involved in eating and sexual behavior) and lateral orbital PFC (risk assessment and adjustment of maladaptive affective states), hypoactivity of the dorsolateral prefrontal cortex (dlPFC), and over-reactivity of the salience network including the amygdala, dorsal anterior cingulate cortex, and insula (Ressler and Mayberg 2007; Hamilton et al. 2012; Chiriţă et al. 2015). Structural and functional alterations in MDD involve areas engaged in the reward system, emotion regulation and decision-making, and attentional resources and control, aberrations of which are believed to be the core of this mental condition and may be considered neurobiological markers of MDD (Hahn et al. 2011). Differences in topography of the late gamma oscillatory response to face-like stimuli seem to reflect (at least, partly) compensatory engagement of distinct brain networks and neuronal resources.

Differences over the left middle temporal gyrus

Clarification of the nature of face tuning in MDD speaks to tailored brain imaging work. Yet, even in the neurotypical population, the topography and communication of the brain networks underlying face tuning to Arcimboldo-like images are largely unknown and the outcome of brain imaging studies is controversial (for recent analyses, see Rolf et al. 2020; Pavlova et al. 2021). Functional near-infrared spectroscopy (fNIRS) conducted in 7–8-month-old infants (by using the preferential looking paradigm) indicates that in response to upright Arcimboldo portraits compared with images of single vegetables (as a baseline), the concentration of oxy-hemoglobin (oxy-Hb) increases in the left (but not right) temporal areas, whereas such effect is absent in response to inverted Arcimboldo images in the temporal areas of both hemispheres (Kobayashi et al. 2012).

Lesion findings in patients show that damage to the right occipitotemporal cortices leaves recognition of Arcimboldo paintings intact, but left-hemispheric lesions lead to deficits in face recognition. For example, patient GG (male, born 1942) with damage to the right occipitotemporal cortex as a result of an ischemic infarct in the area of the right posterior cerebral artery (Busigny et al. 2010) as well as patient DC (male, born 1948) with damage to the right fusiform gyrus, BA 36 (Rivest et al. 2009) were both unimpaired in perceiving Arcimboldo portraits as faces. Yet female patient DF (47 years old) with an acquired damage (as a result of accidental carbon monoxide poisoning at age 34) to the left hemisphere near the top of parieto-occipital sulcus, spontaneously recognized only 1 out of 12 Arcimboldo portraits (Steeves et al. 2006).

Electroencephalography (EEG) indicates that amplitude of the N170 component of the event-related potential (ERP) differs between Arcimboldo portraits and

natural faces in the left (but not right) occipitotemporal region (Caharel et al. 2013). In principal agreement with these findings, the present work points to the middle temporal cortex in the left hemisphere as a key brain area with more pronounced gamma oscillations in response to Arcimboldo-like images in neurotypical as compared with MDD individuals. Fluctuations of gamma oscillations over the left middle temporal cortices appear to reflect engagement of the social brain. The present MEG findings nicely dovetail with our earlier report about ties between face tuning in Arcimboldo-like images and social cognition capabilities as measured by the event arrangement task: This link occurs in neurotypical individuals, but is absent in depression (Kubon et al. 2021). Furthermore, the left middle temporal gyrus is implicated in integration of sensory information, object and face feature integration, recognition, retrieving of meaning, and naming as well as memory functions including encoding and consolidation of information (Braunsdorf et al. 2021; Liu et al. 2022).

Gender/sex impact

MDD is believed to have a skewed gender ratio: approximately twice as many females as males are diagnosed with depression (Neitzke 2016; Salk et al. 2017), though depression in males can be overlooked and underestimated. It is suggested that male and female depression may be of different origins, manifestation, and underlying mechanisms (Albert 2015; Kuehner 2017). The present work was aimed at investigation of gamma oscillatory neuromagnetic activity in response to face-like non-face images in male depression. Earlier, it was shown that no difference in the face sensitivity as compared with neurotypical peers occurs not only in male, but also in female MDD (Kubon et al. 2021). It appears that although no differences in topography of gamma oscillatory activity arise at early stages of information processing, topography of the late gamma response underlying face impression differs substantially in male MDD. This points to recruitment of different networks and neural resources with emphasis on compensatory neurobiological mechanisms in male depression. Clarification of whether similar mechanisms are at work in female depression requires further brain imaging research.

Résumé

The present study uncovers the time course and topography of the low-gamma oscillatory MEG response (30–45 Hz) to social signals such as face-like non-face images in male depression. No difference in the face sensitivity was found between MDD patients and their neurotypical peers, though as in the previous study with independent groups of participants (Kubon et al. 2021), face impressions were differently related to perceptual organization: whereas in MDD individuals, face impressions were positively associated with the perceptual organization abilities, in neurotypical controls, this association was absent. Moreover, although at early processing stages, the gamma oscillatory MEG response to non-face face-like images in MDD and TD individuals is rather similar in terms of the topography and time course, its topography is remarkably different at later stages. This points to engagement of distinct networks and neural resources with emphasis on compensatory neurobiological mechanisms in depression. The primary difference between MDD individuals and their neurotypical peers occurs over the left middle temporal cortices, a part of the social brain, also known to underwrite face feature integration and meaning retrieval. Further tailored MEG work is needed to clarify whether similar brain mechanisms are engaged in female depression. In light of the current COVID-19 pandemic leading to impairments in social interaction and face reading due to mandatory face covering by medical masks (Pavlova and Sokolov 2022a, 2022b), the present findings may be of value for maintaining efficient social interaction in individuals with depression.

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Authors' contributions

MAP conceived and designed the study experiments, and supervised the whole project. JK performed testing. JK and VR under supervision of ANS, CB, and MAP performed MEG recording. JK, VR, ANS, CB, and MAP analyzed the data. MAP, AJF, and CB contributed reagents/materials/analysis tools. JK, AJF, and MAP were involved in patients recruitment, information collection, and analysis. JK and MAP were engaged in controls recruitment. JK and MAP wrote the paper. All co-authors contributed to the writing and editing.

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2.2.1 Supplementary Material

Face tuning in MDD individuals can potentially be influenced by the visual sensitivity toward faces as well as the cognitive decision criterion (i.e., a cognitive bias to see faces based on higher-level expectations; Romagnano et al. 2022). The SDT analysis was used to calculate *d-prime* (sensitivity index) and *beta* (decision criterion; Macmillan and Creelman 2005) for patients with MDD and healthy controls. For this purpose, behavioral data from the MEG study was used (Kubon et al. 2023). MDD individuals differ from TD controls neither in their sensitivity index *d-prime* [MDD, 0.584 ± 0.626; Median (Mdn), 0.329; 95% confidence interval (95 % CI), 0.292–0.877; TD, 0.550 ± 0.538; Mdn, 0.450; 95% CI, 0.305–0.795; Mann-Whitney test U = 204, p = 0.876, two-tailed, not significant, n.s.] nor in the decision criterion *beta* [MDD, 1.070 ± 0.580; Mdn, 0.958; 95% CI, 0.798–1.341; TD, 1.115 ± 0.585; Mdn, 1.000; 95% CI, 0.849–1.381; Mann-Whitney test U = 165, p = 0.240, two-tailed, n.s.].

3 GENERAL DISCUSSION

Both experimental studies presented in this work aimed at the investigation of face tuning in MDD patients compared with person-by-person matched TD individuals. For this purpose, the recently developed Face-n-Food paradigm was used (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; Pavlova et al. 2021). Compared with photographs or portraits of real faces, the Face-n-Food images do not trigger face processing as they do not contain habitual face elements like a nose. The outcome of the initial behavioral study indicated comparable face recognition thresholds and remarkably similar recognition dynamics in MDD and TD individuals (Kubon et al. 2021). Furthermore, no sex/gender differences in face tuning occurred in both investigated groups. However, face tuning in MDD and TD individuals correlated with different cognitive abilities: whereas in TD individuals, it was attached to performance on a social cognition task, MDD individuals exhibited a link between face tuning and visual perceptual organization. Taken together, this implies similar face tuning, but different neural pathways and underlying cognitive and behavioral strategies. Therefore, the question arose whether, and, if so, how altered brain networks may contribute to face tuning in MDD as compared to TD individuals. As MEG yields a high resolution over space and time, this brain imaging technique was used to extend and further clarify behavioral findings (Kubon et al. 2023).

As male depression is currently under-investigated and the MEG study design required a homogenous group of participants, we set our focus on male MDD. The behavioral outcome of the MEG study agrees well with the findings of the behavioral study performed in a separate patient sample and with a different *experimental paradigm*: For MEG, a two-alternative forced-choice (2AFC) paradigm was run, whereas earlier behavioral work was based on an open-end task. Apparently, the latter task is more liberal and thus it appears to be more sensitive toward differences between MDD and TD individuals. Regarding the *presentation mode*, we used a pseudo-randomized order of images during MEG recording and presented them repeatedly (Kubon et al. 2023). In contrast, a single, predetermined series of Face-n-Food images with increasing face resemblance was administered in the behavioral study (Kubon et al. 2021). Again, the

latter approach allowed for better detection of group differences. Despite these methodological differences, the behavioral outcome of both studies points to (i) the intact face tuning in MDD as compared to TD individuals, and (ii) the correlation between face tuning and visual perceptual organization in MDD. This link was absent in the group of person-by-person matched TD individuals.

In order to investigate face tuning at the brain level, we focused on gamma-band oscillatory activity. The gamma frequency range is known to reflect *Gestalt* perception and, therefore, serves as a valuable brain correlate for the investigation of face pareidolia. The MEG analysis revealed similar activation of the occipital brain regions, namely, the medioventral occipital cortex (MVOC) and lateral occipital cortex (LOC) during early stimulus latencies in TD and MDD individuals. However, at later processing stages, gamma oscillatory activity differed in its topography: whereas in TD, face vs. non-face contrast showed activation in the parietal brain areas, MDD individuals exhibited activation in the prefrontal brain regions. This suggests that, despite comparable early face processing, at later processing stages, MDD patients may recruit compensatory neural networks. The main difference between MDD and TD individuals occurred over the left middle temporal gyrus (MTG), one of the key areas of the social brain, responsible for feature integration and meaning retrieval.

In general Discussion (below), the behavioral (psychophysical) and MEG findings will be considered in the context of clinical and neuropsychological MDD phenotype. First, the results will be compared with previous studies, which employed the Face-n-Food paradigm in other neuropsychiatric and neurodevelopmental conditions. In addition, the outcome of both studies will be discussed based on common brain models of depression. Last, but not least, the investigation of neuropsychological disorders requires careful consideration of sex/gender-specific factors. Therefore, the sex/gender specificity of MDD phenotype, face tuning toward Face-n-Food images, and face processing in general will be discussed.

3.1 Comparison with previous studies on face tuning

As previously mentioned, face processing and body language reading show aberrancies in a variety of neuropsychiatric conditions. For depression, a majority of studies point to deficient and negatively biased social perception. However, other studies do not support this outcome and show less severe and more reversible deficits (Weightman et al. 2014). The inconsistency in results may be, at least, partly, attributable to a vast range of administered stimulus types and experimental paradigms. This calls for cross-disease research, which allows better comparison of behavioral findings and associated clinical phenotypes (Pavlova 2017a; Pavlova 2017b; Romagnano et al. 2022).

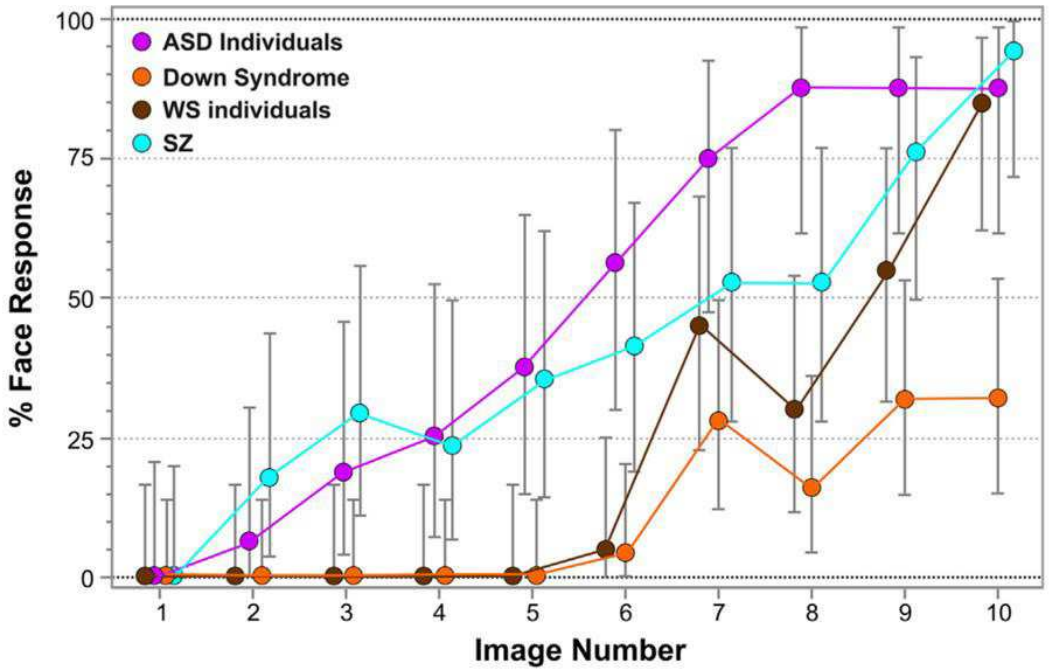

Figure 3. Previous studies on face tuning. Percentage of face responses to the Face-n-Food images for different neuropsychiatric conditions including autism spectrum disorder (ASD, violet), Down syndrome (DS, orange), Williams syndrome (WS, brown), and schizophrenia (SZ, blue). The image number indicates face resemblance (from 1, least recognizable, to 10, most recognizable as a face). Vertical bars show 95% confidence intervals (95% CI). From Rolf et al. 2020; Copyright © 2020 by Elsevier, reprinted with permission of the publisher.

The Face-n-Food paradigm, as used in our behavioral study (Kubon et al. 2021), was first established in a group of TD participants, showing a female advantage in face tuning (Pavlova et al. 2015a). Subsequently, the same experimental paradigm was employed in different neuropsychiatric conditions, including ASD, Down syndrome (DS), Williams

syndrome (WS), adolescents who were born preterm, and SZ (Pavlova et al. 2016a; Pavlova et al. 2017b; Pavlova et al. 2018a; Rolf et al. 2020; Pavlova et al. 2021). Although impairments in face tuning occurred in all so far investigated clinical samples, the severity of deficits as well as recognition dynamics (defined by the form and slope of recognition curves) substantially differed between them (**Figure 3**). For example, individuals with ASD, SZ, and WS (despite lower face sensitivity) consistently saw a face in the last, most face-resembling Face-n-Food image. However, most participants with DS were still non-responsive toward this image as a face (Pavlova et al. 2018a). Keeping in mind that face tuning was deficient in all so far investigated conditions, it appears even more arresting that it was intact in MDD individuals, both in terms of face tuning threshold and recognition dynamics (Kubon et al. 2021).

At first glance, the finding of intact face tuning in MDD seems to contradict the clinically observed difficulties in social functioning. However, it is important to note that mental disorders do not necessarily imply deficient social cognition at all levels of information processing. In fact, the intact face tuning does not necessarily contradict previous findings of negatively biased *affective face processing* in MDD. Whereas unhindered face tuning per se may originate from an intact face detection machinery (early stages of information processing), aberrant affective evaluation may be rooted in higher-level cognitive processes such as rumination and emotion regulation.

As most patients received psychopharmacological treatment at the time of examination, a possible influence of antidepressants on face tuning must be considered. In a group of individuals with depression and/or anxiety, SSRIs decreased insula and amygdala activity during a facial emotion assessment task (Gorka et al. 2019). Furthermore, SSRIs improved eye gaze stability during facial assessment in individuals with high neuroticism levels and fostered recognition of positive facial expressions (Di Simplicio et al. 2014a). However, in the present behavioral study (Kubon et al. 2021), no difference in face tuning occurred between sub-groups of MDD patients with and without SSRI/Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) medication. Additionally, when comparing patients with SSRI/SNRI intake and their matched controls, no significant differences were found. This indicates that antidepressant medication did not substantially affect face tuning.

3.2 Comparable face tuning, but different strategies?

Although MDD individuals showed intact face tuning, the question arises whether they used the same behavioral strategies and underlying brain networks as compared to TD individuals. Many mental disorders including ASD and SZ are characterized by aberrant (social) cognitive functioning, but also by behavioral skills and neuroplasticity, which may compensate these deficits (Mihaljević-Peleš et al. 2019; Livingston et al. 2020).

In our behavioral study, face tuning allied with scores on a social cognition task in TD, but with the visual perceptual abilities in MDD (Kubon et al. 2021). Using a different experimental paradigm, we confirmed that face tuning to upright Face-n-Food images was knotted with visual perceptual organization in male depression (Kubon et al. 2023). Furthermore, MEG analyses revealed differences in brain response during face tuning: whereas both groups recruited the occipital brain areas at early processing stages, later stages revealed activation of the parietal brain regions in TD, but prefrontal engagement in MDD. Taken together, both studies suggest involvement of different behavioral strategies and underlying brain networks during face tuning in TD and MDD.

The MEG findings dovetail with established brain models of MDD, which emphasize the role of the prefrontal areas: The *limbic-cortical componential model* supposes a hypoactivity of the DLPFC (Mayberg 1997). Reduced reactivity of the DC and DLPFC is also vital for the *integrative neural model of heightened salience* and is thought to underlie impaired evaluation of affect in MDD (Hamilton et al. 2012). At the morphological level, brain imaging studies point to a volumetric reduction of the frontal and insula areas (Koolschijn et al. 2009; Lai and Wu 2014; Zacková et al. 2021). Furthermore, aberrancies in the frontal brain networks have been linked with anhedonia, executive malfunctioning, and negatively distorted processing (Pizzagalli and Roberts 2022). The frontal areas (e.g., PFC or OFC) are part of wider distributed neuronal networks in MDD. These networks show hyper- (AN and DMN) or hypoconnectivity (CCN and RN) and may trigger main symptoms of depression such as dysphoria, rumination, cognitive deficits, and anhedonia (Li et al. 2018).

Thus, brain activity during later stages of face tuning may reflect the recruitment of the disease-relevant prefrontal areas in MDD individuals. Apparently, MDD patients may

show an enhanced affective evaluation of the face-like visual input in these areas. Along with the lack of top-down control over limbic structures (Chiriţă et al. 2015), this may cause alterations in the evaluation of social cues. To go one step further, such a (negative) cognitive bias may itself increase responsiveness toward social signals such as faces. However, these assumptions require further experimental proof. For example, connectivity analysis may help to investigate signaling between the occipital visual areas, the face-selective *core network* (i.e., FFA, OFA, pSTS) and the frontal brain regions during processing of Face-n-Food images.

According to the SDT (Macmillan and Creelman 2005), face responsiveness depends on the visual sensitivity as well as cognitive bias (i.e., higher-level disposition to see faces) (Zhou and Meng 2020). A recent study conducted in a group of male SZ individuals demonstrated lower face tuning to face-pareidolic Face-n-Thing images, which was related to lower visual sensitivity (Romagnano et al. 2022). However, no difference in the cognitive bias was found between SZ patients and TD individuals. Conversely, paranormal and religious believers showed no change in the visual sensitivity, but a more liberal cognitive decision criterion (Riekki et al. 2013).

One may ask whether the visual sensitivity and cognitive decision criterion are separately affected by MDD. To account for these possibilities, an additional analysis was conducted based on the behavioral data from Kubon et al. 2023. No differences in the sensitivity index and the decision criterion occurred between TD and MDD individuals (for further details, see **section 2.2.1, Supplementary Material**). Taken together, further research must disentangle the contribution of the visual sensitivity and decision criterion on face tuning in male and female depression.

3.3 Gender differences

MDD has a female preponderance with an estimated sex ratio of 2:1 (Salk et al. 2017). However, this may not only reflect differences in vulnerability but also an underestimation of male depression with consecutively lower diagnostic rates in males (Martin et al. 2013). It is important to consider female and male depression as clinical entities with distinct risk factors and unique symptomatology. Especially male depression

is currently under-investigated and, in the clinical context, remains often undiagnosed (Seidler et al. 2016; Oliffe et al. 2019). With respect to suicidal ideation and high suicide fatality in males, this has drastic implications for affected individuals. Therefore, sex/gender differences are highly relevant for the screening and treatment of MDD, but also for the investigation of pathophysiology. The question arises as to which extent sex/gender influences social cognitive abilities in depression. For the investigation of these sex/gender differences, it is important to note that they may originate from (i) pre-existing differences (i.e., existent before disease onset), (ii) sex/gender-specific disease effects, and/or (iii) an interaction between these factors.

In the domain of face processing, TD females are known to be more proficient in the recognition of facial content, although findings depend on observer age, face familiarity, displayed emotions, and the actor's sex (Kret et al. 2011; Pavlova 2017a; Abbruzzese et al. 2019; Mishra et al. 2019). Most research focuses on sex/gender differences regarding affective face processing. In contrast, findings on face tuning *per se* remain scarce and controversial.

In a group of young neurotypical university students, females outperformed males on the Face-n-Food task (Pavlova et al. 2015a). As compared to their male counterparts, they exhibited lower face tuning thresholds and higher overall face response rates. Only in females, face likability was linked to face resemblance of the Face-n-Food images (Pavlova et al. 2016b). Moreover, sex/gender specificity on the Face-n-Food task was modulated by even subtle cultural factors: In a group of Swiss participants, no sex/gender differences occurred for face tuning. Across cultures, Swiss males excelled in face tuning over their German counterparts, whereas no differences were found between Swiss and German females (Pavlova et al. 2018b).

The outcome of the present work points to comparable face tuning between males and females in MDD as well as TD individuals, which seems to contradict previous findings of female superiority on the same task (Kubon et al. 2021). Nevertheless, face tuning may depend, next to cultural factors, on participants' age, education level, and socioeconomic background. Whereas young female university students excelled over males in face tuning (Pavlova et al. 2015a), this effect may diminish when investigating a more

heterogenous group with a higher age span and, at least, in part, different socioeconomic background (Kubon et al. 2021).

Furthermore, sex/gender-specific performance may vary depending on the experimental procedure: Using a 2AFC paradigm (in contrast to a spontaneous open-end recognition task in Pavlova et al. 2015a) and a different set of face-pareidolia stimuli (Face-n-Thing images), male and female university students showed comparable face tuning toward canonically oriented images (Pavlova et al. 2020). However, in this study, the face inversion effect (FIE; impairment of face impression by stimulus rotation of 180 degrees in the image plane) was less pronounced in females than in males.

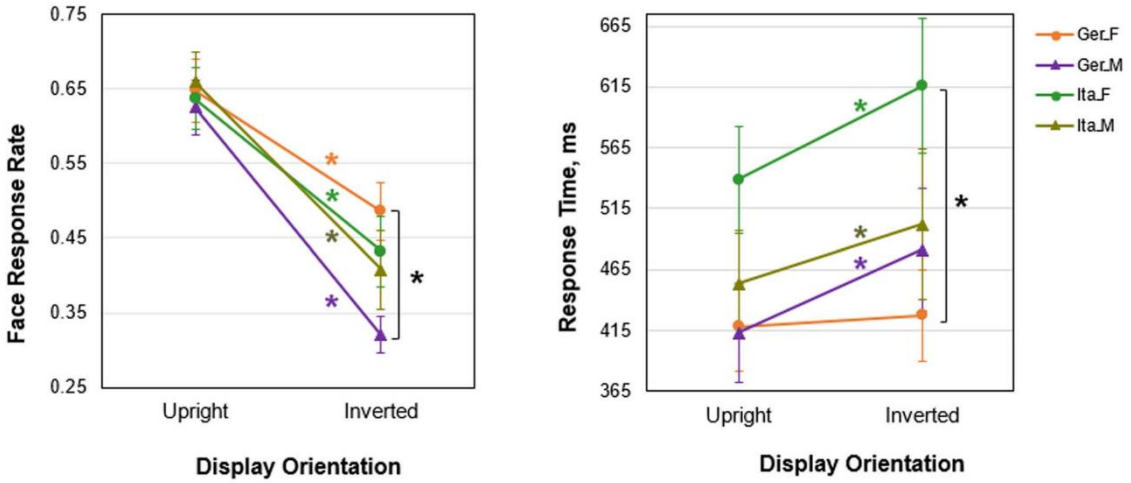

Figure 4. Culture-specific face inversion effect (FIE). Face response rates (left panel) and response times (right panel, in ms) toward Face-n-Thing images in German and Italian females (orange and green blobs) and in German and Italian males (violet and olive triangles). In each graph and for each group, the effect of display inversion is plotted. Vertical bars show the standard error of the mean (SEM). Asterisks represent significant differences ($p < 0.05$) indicated by the corresponding group color. Black asterisks show significant differences in face response rates between German females and German males (left) and in response times between Italian females and German females (right). From Romagnano et al. 2023; Creative Commons Attribution License [CC BY].

Although literature on the FIE in mental disorders is sparse, a recent study found a reduced FIE in male SZ as compared to TD individuals (Romagnano et al. 2022). Intriguingly, the FIE is also modulated by sex/gender and culture (**Figure 4**): In TD individuals, the FIE was more pronounced in German males than in German females. However, this sex/gender specificity of the FIE was absent in Italian participants

(Romagnano et al. 2023). Taken together, further studies should address how sex/gender, culture and/or an interaction between these factors influence the FIE in MDD.

3.4 Résumé

Face tuning and body language reading are two key components of social cognition, which are vital for effective interaction in TD individuals but show aberrancies in a wide range of mental disorders. This work was aimed at the examination of face tuning in MDD as well as of underlying behavioral strategies and neuronal networks. Although the initial work had primarily explorative character, alterations in face tuning had been expected based on previous evidence on deficits in social cognition in MDD. However, contrary to these expectations, in both studies, intact face tuning was observed in MDD individuals. This finding is of high relevance since previous studies showed impaired face tuning toward Face-n-Food images in various mental disorders such as ASD, SZ, and DS. In fact, depressed individuals were the first so far investigated clinical group, which showed intact face tuning (Kubon et al. 2021). However, face processing was knotted to the visual perceptual organization in MDD, but social cognition skills in TD individuals. This outcome dovetails with the findings of the MEG study: While early face processing showed comparable occipital gamma activity in both groups, during later processing stages, the parietal brain areas in TD versus the frontal areas in MDD were recruited (Kubon et al. 2023). Frontal activity in MDD may reflect involvement of disease-specific brain networks and therefore aligns with established brain models of depression. Regarding sex/gender, differences in face tuning between male and female participants occurred neither in the TD nor in the MDD group. The MEG study focused on male depression, a so far under-investigated patient population. Although no sex/gender differences occurred at the behavioral level, future studies should compare brain networks of face tuning in male and female depression. Taken together, this work has important implications for our understanding of MDD pathophysiology and mental well-being under the current post-pandemic conditions.

4 SUMMARY

The present work aimed to clarify face tuning in individuals with MDD. For this purpose, we used Face-n-Food images, which, unlike other commonly used stimuli, do not automatically trigger face processing. In the behavioral study (Kubon et al. 2021), MDD individuals demonstrated intact face tuning and remarkably similar recognition dynamics as compared to TD individuals. Furthermore, sex/gender differences in face tuning occurred neither for MDD nor TD individuals. However, whereas the face sensitivity was associated with performance on a visual perceptual organization task in MDD, it was linked to social cognitive abilities in TD individuals. This suggests different (compensatory) behavioral strategies and underlying brain networks. In a second step, non-invasive brain imaging (MEG, providing for high spatial and time resolution) was used for the investigation of brain circuits underwriting face tuning. As male depression is currently under-investigated and MEG analysis requires a homogenous group of MDD and TD individuals, the focus was set on male MDD. Cutting-edge analysis of time course and topography of gamma oscillatory brain activity during processing of Face-n-Food images was performed. In line with the initial behavioral (psychophysical) study (Kubon et al. 2021), the face sensitivity to upright Face-n-Food images was comparable between MDD and TD individuals. Furthermore, in accord with the previous behavioral study, face tuning was intimately tied with the visual perceptual organization in MDD individuals. Time-frequency representation and subsequent source localization of MEG data revealed comparable topography of gamma oscillators at early latencies with peaks over the visual occipital areas. However, at later latencies, gamma oscillatory activity originated from the parietal brain areas in TD, but frontal areas in MDD. Most important, between-group contrast pointed to the left middle temporal cortex, a part of the social brain, primarily involved in feature integration and meaning retrieval. Taken together, these findings implicate intact face sensitivity to face-pareidolia images as well as preserved early information processing in MDD, resulting from compensatory cognitive strategies and alterations in the underlying brain networks. This work sheds light on the face tuning abilities and social functioning in depression with valuable insights for treatment and remediation of this mental disorder.

5 ZUSAMMENFASSUNG

Diese Arbeit beleuchtet die Gesichtssensitivität in Personen mit unipolarer Depression. Hierfür wurden die Face-n-Food-Bilder eingesetzt, die im Gegensatz zu anderen häufig verwendeten Stimuli nicht automatisch zu einer Gesichtswahrnehmung führen. In der Verhaltensstudie (Kubon et al. 2021) zeigten depressive Individuen gegenüber neurotypischen Kontrollprobanden eine intakte Gesichtssensitivität und vergleichbare Erkennungsdynamik. Darüber hinaus ergaben sich in keiner der beiden Gruppen geschlechtsspezifische Unterschiede. Die Gesichtssensitivität von depressiven Individuen war mit visueller Wahrnehmungsorganisation assoziiert, die von Kontrollprobanden hingegen mit sozial kognitiven Fähigkeiten. Dies deutet auf unterschiedliche (kompensatorische) Verhaltensstrategien und zugrundeliegende zerebrale Netzwerke hin. Zur weiteren Klärung der neuronalen Korrelate wurde in einem zweiten Schritt die Magnetoenzephalographie (MEG) mit hoher räumlicher und zeitlicher Auflösung eingesetzt. Da die MEG-Analyse homogene Teilnehmergruppen erfordert und männliche depressive Erkrankungen unzureichend untersucht sind, lag der Fokus auf diesem Gebiet. Zeitverlauf und Topografie zerebraler Gammaaktivität wurden mittels moderner Verfahren analysiert. Im Einklang mit der ersten (psychophysischen) Studie (Kubon et al. 2021) war die Gesichtssensitivität für aufrecht präsentierte Face-n-Food Bilder zwischen depressiven Individuen und Kontrollprobanden vergleichbar. Erneut ergab sich eine Korrelation zwischen Gesichtssensitivität und räumlicher Wahrnehmungsorganisation in der unabhängigen Stichprobe von depressiven Individuen. Die Zeit-/Frequenzdarstellung und nachfolgende Quellenlokalisation zeigten eine vergleichbare Topografie von Gammaoszillatoren für frühe Latenzen mit Peaks über den okzipital visuellen Arealen. Allerdings ging die Gamma-Aktivität für spätere Latenzen von den parietalen Regionen in der Kontrollgruppe, aber von den frontalen Regionen in depressiven Individuen aus. Eine Zwischengruppenanalyse verwies auf den mittleren temporalen Cortex, einen Schlüsselbereich des sozialen Gehirns, der für Merkmalsintegration und Deutungsvorgänge verantwortlich ist. Zusammengenommen implizieren die Ergebnisse eine intakte Gesichtssensitivität und frühe Prozessierung von pareidolischen Gesichtsstimuli, die auf kompensatorischen kognitiven Strategien und Änderungen in zugrundeliegenden zerebralen Netzwerken beruhen. Diese Arbeit

beleuchtet die Gesichtssensitivität und das soziale Funktionsniveau depressiver Individuen mit wertvollen Einblicken für die Therapie der Erkrankung.

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7 DECLARATION OF CONTRIBUTION

Face Tuning in Depression. Cerebral Cortex (2021), 31(5):2574-2585.

Julian Kubon, Alexander N. Sokolov, Rebecca Popp, Andreas J. Fallgatter, and Marina A. Pavlova

Conceived and designed the study: MAP. Performed the experiments: JK under supervision and presence of MAP. Analyzed the data: MAP, ANS, JK. Contributed reagents/materials/analysis tools: MAP, ANS, AJF. Patient recruitment, information collection, and analysis: RP, MAP, JK, AJF. Control recruitment: MAP, JK. Wrote the paper: JK, MAP. All coauthors contributed to the writing and editing. Supervision and administration of the whole project: MAP.

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Julian Kubon, Valentina Romagnano, Alexander N. Sokolov, Andreas J. Fallgatter, Christoph Braun, and Marina A. Pavlova

Conceived and designed the study: MAP. Performed testing: JK. Performed MEG recording: JK, VR under supervision of ANS, CB, MAP. Analyzed the data: JK, VR, ANS, CB, MAP. Contributed reagents/materials/analysis tools: MAP, AJF, CB. Patient recruitment, information collection, and analysis: JK, AJF, MAP. Control recruitment: JK, MAP. Wrote the paper: JK, MAP. All coauthors contributed to the writing and editing. Supervision and administration of the whole project: MAP.

I hereby confirm that I have written this doctoral thesis on my own and have not used any sources other than those indicated by me.

Tübingen, August 16 2023

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