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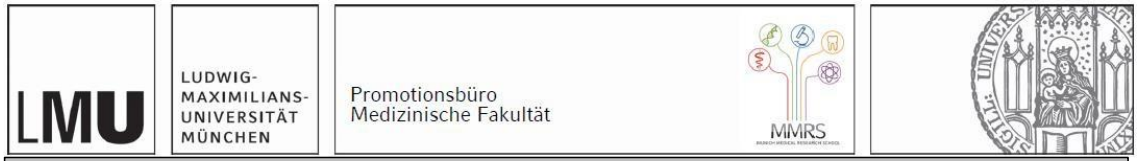

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List of abbreviations

ACC- anterior cingulate cortex

AD – Alzheimer ‘s disease

CMS – cortical midline structures

DMN – default mode network

dmPFC – dorsomedial prefrontal cortex

EE – emotional expression

fMRI – functional magnetic resonance imaging

lParC – lateral paracentral lobule

lPC – inferior parietal cortex

MNS – mirror neurons system

mParC – medial paracentral lobule

PAG – periaqueductal grey matter

ParC – paracentral lobule

PCC- – posterior cingulate cortex

pgACC – pregenual anterior cingulate cortex

SD – self-disturbances

TC – temporal cortex

TMS – transcranial magnetic stimulation

vlPFC – ventrolateral prefrontal cortex

vmPFC – ventromedial prefrontal cortex

List of publications

1. **ZAYTSEVA Y**, Gutyrchik E, Bao Y, Pöppel E, Han S, Northoff G, Welker L, Meindl T, Blautzik J. (2014). Self-processing in the brain: a paradigmatic fMRI case study with a professional singer. // Brain and Cognition, V. 87C, P. 104-108. **IF=2.682**

2. Park M., Gutyrchik E, Welker L, Carl P, Pöppel E, **ZAYTSEVA Y.** Meindl T, Blautzig J, Reiser M, Bao Y. (2015) Sadness is unique: Neural processing of emotions in speech prosody in musicians and non-musicians. // Frontiers in Human Neuroscience, doi: 10.3389/fnhum.2014.01049. **IF=3.473**

3. Silveira S, Bao Y, Wang L, Pöppel E, Avram M, Simmank F, **ZAYTSEVA Y**, Blautzik J. (2015) Does a bishop pray when he prays? Anddoes his brai distinguish between different religions?" PsyCh Journal, 4(4):199-207. doi: 10.1002/pchj.116. **IF=1.559**

4. **ZAYTSEVA Y**, Caroline Szymanski C, Gutyrchik E, Pechenkova E, Vlasova R, Wittmann M. (2015) A disembodied man: A case of somatopsychic depersonalization in schizotypal disorder. // PsyCh Journal, 2015, 4(4):186-98. doi: 10.1002/pchj.115. **IF=1.559**

5. Han KH+, **ZAYTSEVA Y+**, Bao Y, Pöppel E, Chung SY, Kim JW, Kim HT. (2014) Impairment of vocal expression of negative emotions in patients with Alzheimer's disease. // Frontiers in Aging Neuroscience, 26:6 doi: 10.3389/fnagi.2014.00101. **IF=5.702**
+ equally contributing authors

1. Short summaries and contribution to the publications

1.1 In my doctoral thesis, I will provide insight into the various aspects of self-processing in the brain and how it intervenes with emotions and memory. The thesis is divided into five parts. Behavioural and experimental neuroimaging studies were performed in Germany, the Russian Federation, and the Republic of Korea from 2012 to 2015.

1.2 The first part (ZAYTSEVA Y. et al. (2014). ‘’Self-processing in the brain: a paradigmatic fMRI case study with a professional singer’’ // Brain and Cognition, V. 87C, P. 104-108) tests the hypothesis on the differential involvement of the midline brain structures in self-referential and self-related processing and how the eminent professional identity may highlight the differences and gives the ability to spot both processes in one case. Contribution to the paper: I have conceptualized the study results, performed the fMRI analysis, wrote the manuscript draft, and proceeded with the submissions and all rounds of revision.

1.3 The second part (Park M. et al. (2015) ‘’Sadness is unique: Neural processing of emotions in speech prosody in musicians and non-musicians’’. // Frontiers in Human Neuroscience, doi: 10.3389/fnhum.2014.01049) investigates the perception of emotions in speech and how professional identity and a musical training affects it. Contribution to the paper: I have participated in the study design and interpretation of the study results, revised the manuscript, its methods, and results, and added the points to the discussion.

1.4 The third part (Silveira S. et al. (2015) ‘’Does a bishop pray when he prays? And does his brain distinguish between different religions?" PsyCh Journal, 4(4):199-207) comprises the investigation of the self-referential processing in a catholic bishop while perceiving contextual religious texts. Contribution to the paper: I have participated in the study design, data acquisition, and interpretation of the results. I have revised the manuscript, its methods, and results and added the points to the discussion.

1.5 In the fourth part (ZAYTSEVA Y. et al. (2015) ‘’A disembodied man: A case of soma-to-psychic depersonalization in schizotypal disorder’’. // PsyCh Journal, 2015, 4(4):186-98), a case of the soma-to-psychic depersonalization is presented, and the relation between the self-processing in tactile perception is discussed. Contribution to the paper: I have designed the study and performed the clinical, neuropsychological, and behavioural assessment. I have designed and performed the fMRI experimental paradigm. I analysed

the behavioural and fMRI data and performed the statistical analysis. I have written the draft of the manuscript and proceeded with submissions and revisions of the paper.

1.6 In the fifth part (Han K.H., ZAYTSEVA Y. (2014) ‘’Impairment of vocal expression of negative emotions in patients with Alzheimer's disease’’. // Frontiers in Aging Neuroscience, 26:6 doi: 10.3389/fnagi.2014.00101), the impairment of vocal expression in Alzheimer's disease and possible effects on the identity are highlighted. Contribution to the paper: I have performed the statistical analysis, wrote the paper draft, and proceeded with the submissions of manuscript revisions. The first authorship was divided between Dr. Kyung-Hun Han. Dr. Han collected the data in the Republic of Korea; further analysis and manuscript drafting was performed in Munich.

2. Introduction

What if the Self is likened to a flock of birds? They soar through the sky, maintaining harmonious synchrony with the shifts in the air. However, when communication between the birds is disrupted, so too is the unity of the flock. At a certain point, we can no longer refer to it as a flock. Similarly, the Self implies an inner organizing principle.

2.1. Concepts of the Self

The conceptualization of the self has been one of the most prominent issues in the fields of philosophy, psychology, and neuroscience. Esteemed scholars such as Popper (1977), Damasio (1999), Gallagher (2000), Gallagher & Frith (2003), Metzinger & Gallese (2003), and Northoff (2004) have extensively explored this subject. Despite the long theoretical discourse and many experimental studies, no settled terminological system in the neurocognitive research of the self has been established. Terms such as self-processing, self-related, self-referential, self-relevant, and self-reflective processing are used interchangeably across published papers. Moreover, to distinguish different aspects of the processing of self, more recent terms have been proposed, such as self-specifying processing. Here we will shed some light on the similarities and differences between these terms and define the terms used in the thesis.

Drawing from theoretical assumptions and empirical evidence, scholars have identified two distinct subtypes of the self. One subtype is known as the "mental self" (James, 1890), "narrative self" (Gallagher, 2000), or "autonoetic consciousness" (Keenan et al., 2000), encompassing higher-order cognitive processes and representing an external point of view. The narrative self is viewed as a self that encompasses an “individual identity” (Gallagher, 2000) with a variety of specific experiences and values and ‘’personal and interpersonal forms of narrative activity’’ that are integrated into the coherent self-concept (Zahavi, 2007. In this context, episodic memory serves to synchronize the past and present "selves," thereby creating a coherent and subjectively continuous self-identity over the course of one's life(Bao et al., 2015).

Alternatively, a different concept of the self has been advocated that focuses not on higher-order cognitive but basic somatic and affective functions. This concept aligns more closely with an internal point of view of oneself. This lower-order concept of the self is often referred to as the "corporeal self" or "bodily self" (Pribram, 1999) or "proto-self" (Panksepp, 1998). Additionally, the minimal self is defined as a sense of self intrinsic to any conscious state (Gallagher & Zahavi, 2012; Zahavi, 2016).

A primitive form of self-reference, known as a "sense of mineness," makes our experiences conscious by allowing us to recognize that the experience belongs to us personally. This concept is often associated with the notion of pre-reflective self-consciousness, which

indicates an inherent awareness of the self before any reflective thought. Within this framework, the existence of a minimal self is independent of linguistic and conceptual abilities, being realized primarily through sensory and motor domains. This concept underscores that the minimal self emerges from basic, non-verbal interactions with the environment, highlighting its fundamental nature.

Regarding the relationship between the two types of the self, this perspective asserts that the minimal and narrative selves are complementary but distinct aspects of selfhood. Self-awareness is considered a prerequisite for the emergence of the narrative self. While these two aspects are typically integrated, in clinical cases involving a significant deficit in the narrative self, such as the advanced stages of Alzheimer's disease, only the minimal self may remain. In such instances, without the ability to reference the past within the present, a patient may lose their sense of identity, as they can no longer recognize their personal narrative reflected in episodic memory. Consequently, the synchronization of past experiences within a present time frame might be considered a neural foundation for personal identity.

2.1.1. Self-referential and self-related processing

The terms "self-referential" and "self-related," introduced by Northoff et al. (2006), have served as a framework for building up experimental paradigms using brain imaging.

Self-referential processing involves the cognitive handling of stimuli that are perceived as being closely related to one's own identity and personal experiences. Typical examples include how we perceive images of ourselves or close friends compared to pictures of strangers, or how we respond to images of the houses where we spent our childhood versus pictures of unfamiliar houses. These comparisons can be observed across various sensory modalities (Northoff et al., 2006), highlighting the profound impact of personal relevance on our perception and cognition. In this case, the strength of a stimulus's relationship to the self unifies and categorizes inputs, not their sensory origin (as Kircher and David, 2003). The concept of "mineness" regarding self-stimulus depends heavily on the specific context, encompassing autobiographical, social, spatial, and a myriad of other pertinent factors. This term encapsulates how individuals perceive and assert their identity and experiences.

The self-referential aspect typically involves a heightened emotional subjectivity, wherein stimuli are imbued with significant personal value. When perceived through the lens of the self, these stimuli cease to be mere objective elements of the universe; instead, they take on emotional hues and become deeply intertwined with one's sense of identity. Additionally, the self is shaped by both physical and psychological stimuli. Physical stimuli include sensory inputs from the body like facial expressions, sensations, and internal bodily processes. In contrast, psychological stimuli encompass one's conceptual understanding of oneself, such

as episodic memories, and complex evaluations like body image and self-worth (Gillihan and Farah, 2005).

A key distinction between self-referential and non-self-referential attitudes, as highlighted in the literature, is encapsulated by the idea that "the emotional stance towards an object or thought defines the boundary between self and non-self" (Newen, 2018). This emphasizes that personal emotional engagement plays a pivotal role in delineating what is perceived as part of one's self versus external to it.

In their later works, Northoff et al. (2011) add a concept of self-related processing which refers to a fundamental process that creates a relationship between the organism and stimulus. Self-related processing cannot be equated either with the self as subject or with the self as the object (subjective/phenomenological, objective/neuroscientific concepts of self); it also cannot be equated with any different contents (neither with self-specific nor with non-self-specific; neither with subjective/experiential nor with objective/observational); self-related processing makes these distinctions first and foremost possible (Me). It differs from its cognitive counterpart, self-referential processing, which regards the contents—whether bodily, mental, or autobiographical—as given and pre-existing (Northoff, Qin, & Feinberg, 2011).

2.1.2. Neural correlates of the self-processing

Various studies aimed to localize the self's neurobiological correlates by applying various approaches (Northoff, G. & Bermpohl, F, 2004). The findings have been identified mainly in the medial frontal and posterior limbic areas, called cortical midline structures (CMS) (Northoff et al., 2006). CMS are parts of the default-mode network (Gusnard et al., 2001; Raichle et al., 2001, 2007), which itself has been linked to various self-related processes such as self-projection (Buckner et al., 2007), episodic memory (Spreng et al., 2009), or self-generated thought (Andrews-Hanna et al., 2014). Anterior CMS involvement is documented in various studies of attribution of personal trait adjectives to oneself (Araujo et al., 2013; Fossati et al., 2003; Johnson et al., 2002), also with a distinction for emotional and cognitive aspects (Moran et al., 2009) and emotional valence (Williamson et al., 2019). Self-recognition studies focus on the representations of own body and underscore different areas, such as right-lateralized networks of inferior parietal and occipital regions, for visual self-recognition (Deveu et al., 2007; Sigiura et al., 2005; Uddin et al., 2005), superior temporal cortex in voice-recognition (Fu et al., 2005), or inferior frontal cortex for both (Kaplan et al., 2008). The inferior frontal and parietal areas are essential hubs in the mirror-neuron system (MNS) that unifies the perception and execution of actions and forms a platform for understanding observed actions of others from within by their internal simulation (Iacoboni & Dapretto, 2006; Keysers et al., 2010). Central self-processes are subserved by the activity of (at least) these

two main networks- the default mode network and, more precisely, CMS linked to conceptual self-processes and by mirror neuron system (MNS) constituting perception-action grounding. The interaction of both networks is probably in play in self-relevant processing and can be crucial depending on the task employed, as observed in self-other recognition studies (Justen et al., 2014; Qin et al., 2011; Sandrone et al., 2013). However, another line of thought encompassing theories based on the free-energy principle suggests that multimodal bodily representations are not tied to a specific brain area (Apps et al., 2014). The unity and integration of different brain regions are important for providing contextual information that can directly influence how a unimodal signal is experienced (Limanowski et al., 2013).

When examining stimuli specific to self versus non-self, brain imaging research has identified alterations in neural activity within several medial cortical areas, such as the pregenual anterior cingulate cortex (pgACC), dorsomedial prefrontal cortex (dmPFC), and posterior cingulate cortex (PCC) (see reviews by Northoff et al., 2009; Feinberg, 2011). These findings underscore the distinct patterns of brain activation associated with processing information related to one's self versus external entities.

Moreover, numerous studies have consistently shown that the anterior cingulate cortex (ACC), among other regions in the medial cortex (detailed below), plays a significant role in processing stimuli specific to the self (D'Argembeau et al., 2005, 2007; Feinberg & Mallat, 2016; Feinberg, 2011; Gusnard & Raichle, 2001; Han et al., 2009; Modinos et al., 2009; Ochsner et al., 2005; Zhu et al., 2007). Beyond these medial cortex regions, additional brain areas such as the ventrolateral prefrontal cortex (vlPFC), dorsolateral prefrontal cortex (dlPFC), lateral parietal cortex (lPC), bilateral temporal poles, insula, and subcortical regions including the brainstem, colliculi, periaqueductal gray (PAG), and hypothalamus/hypophysis, have also been observed to be active during tasks involving self-referential processing (Northoff et al., 2006).

2.1.3. Self-processing and memory

The process of memorizing, involving the encoding and retrieval of self-referential stimuli, is intricately linked to episodic and autobiographical memory. Studies that approach the connection between self-processing and memory can be divided into two groups. The first group of studies investigated the encoding and retrieval of visually presented self- and non-self-related adjectives describing personality traits. Macrae et al. (2004) studied the retrieval of trait adjectives associated with dorsomedial prefrontal cortex (dmPFC). In Fossati et al. (2003), similar activation in the dmPFC was observed during the encoding and retrieval of positive and negative self-relevant personality traits. The study indicated that both processes—encoding personal traits and successfully retrieving them—involved activation in the right dmPFC. According to the authors, this recruitment of the dmPFC suggests that

self-referential processing is pivotal in connecting personality descriptors to one's self during both the initial encoding and subsequent retrieval phases. To better understand the retrieval of trait adjectives relevant to oneself, Lou et al. (2004) conducted a task-related and connectivity analysis (the best friend, the Danish queen).

They found the activations in DMPFC, PCC/precuneus, right and left inferior paracentral lobule (ParC), left vlPFC, and middle temporal cortex (incl. hippocampus). In addition, connectivity analysis has identified the following connections: dmPFC – mParC, PCC, precuneus; anterior CMS – inferior frontal cortex, inferior paracentral lobule, middle temporal cortex. Drawing from a complementary TMS study, the authors propose that the MPC serves as a central region facilitating interaction between the CMS and other lateral cortical areas during the episodic retrieval of self-referential adjectives. This suggests a pivotal role for the MPC in integrating cognitive and memory processes related to self-relevant information. The second group of studies used the autobiographical memory task (Fink, 1996; Maddock, 1999, 2003; Piefke et al., 2003; Gilboa, 2004), and all identified similar activation in dmPFC and vmPFC.

2.1.4. Self-processing and emotions

Self-processing is tightly bound to emotions. Several research studies exploring emotions have shown activation of the VMPFC, ACC, and DMPFC in the anterior CMS (see Phan et al., 2002 for an overview). This involvement of anterior CMS during emotion processing might indicate simultaneous self-referential processing. Some studies looked at the dissociation between emotion and self-referential processing to address this question. Phan et al. (2002) aimed to appraise the extent of personal association with emotionally salient pictures. Self-referential processing was associated with the activation of CMS (including VMPFC, PACC, and DMPFC), insula, and nucleus accumbens. Regions specifically activated to subjective emotional intensity ratings included the amygdala, the nucleus accumbens, and the insula; these regions differ from those associated with self-relatedness appraisal (see above). In their experiment, Fossati et al. (2003) asked the participants to judge whether positive and negative trait adjectives described themselves adequately. They identified the activations in dmPFC and PCC as related to self-referential processing. Ochsner et al. (2004) compared self-focus and situation-focus of visually presented negative emotional pictures; judged the valence of their emotional responses to pictures or the emotion expressed by the person in a picture. The neural processing of the self-focus was comprised of the activity of PCC/ACC, whereas the situation focus was associated with the activation of the right and left LPFC (VLPFC, DLPFC). These findings are in line with earlier studies (Gusnard & Raichle, 2001) where attention to self-referent emotional conditions induced neural activity in PCC/ACC, VMPFC, and DMPFC when compared to externally cued attention. The activation of mPFC

was connected to the processing of one's own emotions, and the emotional reaction of the person in the picture was related to the activation of lPFC (see Wicker et al., 2003). The authors observed overlap between feeling and seeing of disgust in ACC and insula). Another study indicated that self-referential processing in the emotional domain especially involved the anterior CMS (Northoff et al., 2006).

Thus, there is an intertwining of emotional processing and self-referential processing. While self-referential processing is linked with the default mode network (CMS), emotional processing predominantly occurs in subcortical and other cortical regions, such as the insula, amygdala, brainstem, colliculi, and periaqueductal gray (PAG) (see also LeDoux, 1996, 2012; Panksepp, 1998, 2005; Damasio, 1999; from Northoff et al., 2006). The observed activation in the anterior CMS during emotional processing across different types of emotions and various induction methods (Phan et al., 2002; Murphy et al., 2003) indicates a strong association with self-referentiality that transcends intrinsic emotion processing. This is further supported by findings showing a significant correlation between neural activity in the anterior CMS and emotional valence (Anderson et al., 2003; Small et al., 2003; Heinzel et al., 2005), suggesting that the evaluation of emotional content inherently involves self-reference (Northoff et al., 2006).

2.2. Self-processing in schizophrenia and schizophrenia spectrum disorders

Schizophrenia is a complex disorder that evades a simple definition because it has various facets and expressions. Some patients describe hallucinations, some report only delusions, while other forms of schizophrenia manifest solely by negative symptoms. In many foundational texts (Kraepelin E. (1896), Schneider K. (1947), Mayer-Gross W. (1932)), the core unifying attribute of the disorder was described as self-disturbances (SDs, Bleuler, 1950). Kraepelin (1896) characterized schizophrenia as a "loss of the unity of consciousness" or an "orchestra without a conductor." German psychiatrists like W. Mayer-Gross (1932), H. Gruhle (1932), and K. Schneider used the term Ichstörungen referring to "splitting and weakening of the I is binding of self-components" (Mishara, 2014). Other concepts stressed the role disparity between (splitting of) cognitive and emotional domains (Gruhle, 1932). Kurt Schneider (1947) had a pragmatic approach to using the term Ichstörungen. For him, it referred to the disturbance of "me," "I," and "mine" that is reflected in the first-rank symptoms depicting the aberrant changes of experiencing oneself and own agency. His notion was an extension of Jaspers' criteria of the conscious "I" as having the following properties: demarcation between self (me) and non-self (not me); unity of experience at a given moment and also during time; experience of mine-ness and own existence (Spitzer,1988). Wolfgang Blankenburg (1969) proposed that in Ichstörungen, a

feeling of a change of relationship to self and others emerges. The experience of both oneself and others is disrupted because of a collapse of reference frames, and this disruption is reflective, involving a higher-level thinking process. A person with schizophrenia cannot change one's perspective and take someone else's perspective, similar to being immersed in ongoing processes in a dreaming state. The self is based on the binding of components, a point of intersection (Mishara,2013).

We have described various conditions in which alternations of the experiences on the level of the minimal self are probably present. However, these are indirect indications of SDs since they have not been addressed directly. Their common theme is a destabilizing loss of homeostatic control; the subjective experience of self-disturbances might express a tag of such disintegration. The homeostatic imbalance concerns the prefrontal cortex regions playing a role in cognitive control and more reflexive subcortical areas, as in stress disorders or during adolescence. Similarly, in psychedelic intoxication, we see changes in brain entropy linked to an attenuation of control of the default mode network freeing the activation in other areas that were previously suppressed. It seems that, as well as in schizophrenia, in the psychedelic state, the Ego and structure of perception-action schemes are disturbed more profoundly, accompanied by a misperception of the external world. Self-disturbances reflect the scope of the instability of schemes linked by brain entropy. On the other hand, we see indications of SDs also in, for instance, depression, where the entropy should be low. Does that mean that SDs would be connected to deviation from a balanced state, whichever direction it would be?

In attempts to delineate SDs, the difference between the minimal and narrative self is often underlined (Nelson et al., 2014). The Ipseity disturbances model (Sass, Parnas, 2003; Nelson, 2014) supposes that in schizophrenia, the immediate level of self-experience is affected primarily. The notion of the double dissociation between the minimal and the narrative self is supported by an example of patients with a dissociative personality disorder, who lack the continuity of the narrative self but, simultaneously, their minimal self-experience is usually intact. However, this separation might not genuinely reflect what is going on. Many aberrant processes related to self-experience can occur in the grey zone between these two counterparts. As A. Mishara and M. Schwartz (2013) put forwards, in schizophrenia, both levels are intertwined. Patients often manifest disturbances in the narrative self, as if the I is impaired (also) on the reflective level of binding information. What is lacking is the ability to form a perspective, either one's own or someone else's perspective. We can speak about the minimal and narrative self for a more detailed demarcation of concepts. However, these levels are just endpoints of neural hierarchy, and the mutual influence between these levels is complex. Sass and Parnas' example (2003) of dissociative personality disorder shows that separating the minimal and narrative self is possible but does not pertain to schizophrenia.

Typically, we would imagine that in schizophrenia, the primary perceptual processes are disrupted first, possibly preceding the full onset of the disorder as in prodromal states. Consequently, the sense of identity and self-narrative is eroded. The neural correlates are probably linked to long-term neural changes (excessive pruning, thinning of cortices, neural connectivity changes) that influence the immediate sensory experiences and thus create perceptual ambiguity that might also be experienced on the subjective level as a self-disturbance and be metacognitively evaluated.

The schizotypal disorder does not seem to differ from schizophrenia in SDs (Raballo et al., 2011). However, subclinical individuals who scored in schizotypal traits have higher SDs than individuals with no such traits, supported by similar studies (Raballo et al., 2011). Also, non-psychotic family members of schizophrenia patients score higher on SDs. Importantly, SDs are present not only during the acute phase of schizophrenia but also in remission, and this long-term change should be the disease's hallmark (Parnas et al., 2003). Therefore, such results support the notion of SDs being linked to the whole schizophrenia spectrum having a trait-like character.

Depersonalization disorder resembles self-disturbances found in schizophrenia, most importantly diminished self-affection and changes in the experience of the world and meaning (Sass, 2014). However, it has been pointed out that the symptoms of the Schneiderian first-rank type are experienced less intensively ("as if") (Sass, 2014). According to another study (Varnes et al., 2013), anomalous self-experiences in depersonalization disorder might reflect somewhat compensatory secondary mechanisms, whereas, in schizophrenia, they are more profound with earlier onset.

2.3. Self-processing through the prism of art

A deeper exploration of the self and personal identity can be achieved through the lens of artworks. Art has been proposed to engage specific brain networks associated with various aspects of aesthetic experience. The pleasure and positive emotions evoked by artistic encounters are linked to the brain's reward circuitry, which includes both cortical and subcortical regions. Key areas involved in this process include the orbitofrontal cortex and ventromedial prefrontal cortex, known for their roles in reward processing and the assessment of beauty and aesthetic appeal. The anterior cingulate cortex is implicated in preferences and liking across different artistic domains, reflecting an individual's subjective feelings. The insular cortex, long associated with self-referential processes and emotional experiences, also plays a significant role in artistic appreciation. Additionally, the nucleus accumbens contributes to the generation of positive emotional responses and is involved in evaluating the emotional significance of artworks (Cela-Conde et al., 2013; Cinzia & Vittorio,

2009; Ishizu & Zeki, 2011; Jacobsen et al., 2006; Kawabata & Zeki, 2004; Nadal, 2013; Vartanian & Goel, 2004).

According to Vessel and colleagues (2012), specific regions within the default mode network (DMN) play a critical role in aesthetic experiences, especially during intense emotional responses. While activity in areas like the striatum showed a linear correlation with participants' subjective ratings of aesthetic appeal (indicating how deeply they were affected by the artwork), DMN activity increased in a stepwise manner only in response to artworks rated highest in an fMRI study (Vessel et al., 2012). The researchers suggest that these activations indicate that highly impactful aesthetic experiences involve self-referential processes that are strongly influenced by the personal significance of the artworks. Overall, these studies underscore that aesthetic experiences are driven by stimuli and are subjective processes characterized by powerful emotional reactions, prominently featuring self-related and mind-wandering processing.

Exploring self-processing through the prism of art in neuroscience reveals how artistic experiences engage neural mechanisms associated with self-reflection, emotion, and subjective meaning-making. This intersection offers insights into how the brain integrates aesthetic encounters to shape personal identity and emotional responses.

3.Summary

The self is studied in depth in psychology and neuroscience, yet there is no universally recognized definition of what the self is or could be. A new integrative theoretical model of neural mechanisms of the self was introduced based on empirical findings: cortical midline structures (parts of the default mode network) of the brain are involved in the processing of stimuli that refer or relate to the self. Specifically, "self-referential" represents an external point of view while "self-related" means an internal point of view. It is assumed that the components of the self should be viewed as constituents and functions of complex networks rather than as distinct identities.

In a series of studies, we aimed to link self-referential and self-related processing with neural activity. We employed both single studies and group designs. Individuals whose professional identity was notable and distinctive (a famous opera singer, a catholic bishop) represented single cases. In contrast, the clinical case illustrated an example of disordered basic self-processing (depersonalization case). Using a single case approach, we avoided the inter-subject heterogeneity in a group, allowing us to focus on the intricacies deriving from that individual's unique background and epigenetic influences. The focus of the group studies was on the role of emotional processing in individuals with Alzheimer's disease who had a memory impairment that compromised their identity, as well as how musical training could

intensify emotions by engaging in self-referential processing (neural processing in musicians vs. non-musicians).

We identified the cortical midline structures as being involved in self-referential and self-related processing in diverse ways. Specifically, self-referential processing was associated with activations in cortical midline structures (DLPFC, ACC, OFC) in the case of an eminent opera singer. The activation of the precuneus and subcortical structures drove the self-related activity. At the same time, the role of the default mode network was highlighted as being disinhibited in a depersonalization case or during praying in a religious case. The association between self-referential processing, emotions, and memory was demonstrated in group studies. Thus, emotional expression deficit in Alzheimer's patients was closely linked with a decline in autobiographical memory, consequently affecting personal identity. In musicians, the emotional perception was intensified and presumably became more self-referential as the frontal midline structures were more activated in contrast to non-musicians. Art and pathology can provide insight into the neural processing of the self as the cases allow us to naturally model self-processing relying either on protrusive or diminutive features.

4.Zusammenfassung

Das Selbst wird in Psychologie und Neurowissenschaften intensiv untersucht, doch es existiert noch keine allgemein gültige Definition, was das Selbst ist oder sein könnte. Es wird ein neues integratives theoretisches Modell für neuronale Mechanismen des Selbst auf der Basis von empirischen Befunden vorgeschlagen: Kortikale Mittellinienstrukturen des Gehirns (Teile des Ruhenetzwerks) sind an der Verarbeitung von Reizen beteiligt, die in einer Referenz („self-referential“) zu oder in einer engen Verknüpfung („self-related) mit dem Selbst stehen; „self-referential“ bezeichnet eher einen externen Standpunkt zu sich selbst; „self-related“ bezeichnet einen eher internen Standpunkt. Es wird davon ausgegangen, dass Komponenten des Selbst als Bestandteile und Funktionen komplexer Netzwerke und nicht als eigenständige Entitäten zu verstehen sind. In mehreren Studien war das Ziel, die Verarbeitung der beiden Selbst-Modi in einen Zusammenhang mit neuronalen Aktivitätem zu bringen. Es wurden sowohl Einzel- als auch Gruppendesigns genutzt, und Personen mit einer akzentuierten Identität aufgrund des Berufs oder der Beschäftigung oder auch mit Störungen des Selbst aufgrund klinischer Pathologie (Schizophrenie, Morbus Alzheimer) wurden eingeschlossen. Personen mit bemerkenswerter und ausgeprägter beruflicher Identität (eine berühmte Opernsängerin, ein katholischer Bischof) stellten Einzelfälle dar, und ein klinischer Fall diente als Beispiel für eine grundlegend gestörte Selbstverarbeitung (Depersonalisation). Durch die Verwendung des Einzelfallansatzes wurde eine interindividuelle Heterogenität der Gruppe vermieden, was ermöglichte, sich auf besondere Feinheiten zu konzentrieren, die sich aus der einmaligen Beschaffenheit und epigenetischen Einflüssen eines Individuums ergaben. Der Fokus in den Gruppenstudien lag auf der Rolle der Emotionsverarbeitung bei Personen mit Morbus Alzheimer mit einer Gedächtnisstörung, die ihre Identität beeinträchtigte, sowie darauf, wie ein musikalisches Training Emotionen intensivieren kann, indem es selbst-referentielle Verarbeitung nutzt. Es wurde festgestellt, dass kortikale Mittellinienstrukturen auf verschiedene Weise bei den beiden Selbst-Modi beteiligt sind. Insbesondere war die „self-referential” Verarbeitung mit Aktivierungen in kortikalen Mittellinienstrukturen (DLPFC, ACC, OFC) bei der berühmten Opernsängerin verbunden. Die „self-related“ Aktivität wurde durch Aktivierungen im Precuneus und subkortikalen Strukturen beobachtet. Gleichzeitig wurde die Rolle des enthemmten Ruhenetzwerks bei einer Depersonalisation oder während eines religiösen Gebets festgestellt. Ein Zusammenhang zwischen „self-referential“ Verarbeitung, Emotionen und Gedächtnis wurde in den Gruppenstudien nachgewiesen. Das emotionale Ausdrucksdefizit bei bei Morbus Alzheimer war eng mit dem Nachlassen des autobiografischen Gedächtnisses verbunden, was sich auf die persönliche Identität auswirkte. Bei den Musikern war die emotionale Wahrnehmung intensiviert und wurde vermutlich stärker „self-

referential“, da die frontalen Mittellinienstrukturen im Gegensatz zu Nichtmusikern stärker aktiviert waren. Insgesamt läßt sich sagen, daß Kunst und Pathologie besondere Einblicke in die neuronale Verarbeitung des Selbst erschließen; in solchen Fällen ist es möglich, auf eine besondere Weise die Selbstverarbeitung zu untersuchen und zu modellieren.

Summary of paper I

The first part of the thesis, published as Zaytseva et al (2014), was intended to demonstrate cortical midline regions' differential role in self-processing. E.M., a 69-year-old professional soprano singer with over 35 years of experience, is now a professor of singing. The professional Self is a one-of-a-kind self, and the sound of a voice is a one-of-a-kind self that firmly determines her social identity. Her professional specialty has an impact on her identity. An eminent vocalist with extensive long-term professional experience and a solid social identity is a good illustration of how to show how self-oriented processes are interconnected. We expected that self-related and self-referential processing would assemble the hierarchy in the Self's constitution.

The distinction between Self and Other (self-related activity) is aided by activating the precuneus and subcortical structures, which maintain sensory integration of stimuli to the personal context and conform to low-order bodily functions. High-order cognitive processes (frontal midline structures) such as the representation of self-related stimuli, assessment (emotional and moral judgment), and performance monitoring generate self-referential activity. The fact that EM has a solid professional identity aided self-recognition, appraisal, monitoring procedures, and the discovery of internal self-related processing. Self-processing is variably implicated in cortical midline regions, presumably hierarchically related.

We also offer the assumption of the hierarchy of self-processing by using active and passive conditions. The active and passive involvement of the ‘’lower- and higher-order notions’’ of the Self can likewise be separated experimentally. The ‘’lower-order Self’’ is regarded as more passive because it does not necessitate an explicit representation of the selfless; it is thus ‘’presumably related to sensory and motor functions’’, or ‘’more broadly to more bodily functions rather than cognitive processes’’, and is regarded as internally-oriented self-relatedness. The higher-order self is called an "active self" since it necessitates ‘’evaluation and judgment, and explicit conscious awareness’’.

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Case History Study

Self processing in the brain: A paradigmatic fMRI case study with a professional singer

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ABSTRACT

Understanding the mechanisms involved in perception and conception of oneself is a fundamental psychological topic with high relevance for psychiatric and neurological issues, and it is one of the great challenges in neuroscientific research. The paradigmatic single-case study presented here aimed to investigate different components of self- and other-processes and to elucidate corresponding neurobiological underpinnings. An eminent professional opera singer with profound performance experience has undergone functional magnetic resonance imaging and was exposed to excerpts of Mozart arias, sung by herself or another singer. The results indicate a distinction between self- and other conditions in cortical midline structures, differentially involved in self-related and self-referential processing. This lends further support to the assumption of cortical midline structures being involved in the neural processing of self-specific stimuli and also confirms the power of single case studies as a research tool.

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1. Introduction

Theoretical discourse and experimental studies on the *self* in contrast to *others* have a long tradition in scientific debate (for review see: Stich & Warfield, 1994), but no generally accepted understanding exists on what the self is or might be. Neuroscientific research deepened the understanding of the self by using neuroimaging methods which identified the midline of the brain as an area crucially involved in self processing. Differential involvement of cortical midline structures has been proposed by Northoff and Bermpohl (2004) where the areas of the brain carry out specific processes associated with the self, notably, the orbito-medial prefrontal cortex (OMPFC) referred to as representation and labeling of stimuli as self-referential/self-related. Dorsomedial prefrontal cortex (DMPFC) serves as a function of evaluation or judgment of self-specific stimuli. Anterior cingulate cortex (ACC) is associated with monitoring and control function of the self stimuli, specifically paying attention to error detection and performance monitoring. Eventually, posterior cingulate cortex (PCC) and precuneus provide integration or linkage of the stimuli with the personal context (see Northoff & Bermpohl, 2004). However, the proposed model doesn't specify the interaction between four sub-processes, although they might represent a hierarchical structure of the self.

Ordinarily, self-referential processes that constitute the model are studied separately and are considered from various perspectives. Based on empirical findings, two different subtypes of the self have been suggested. On the one hand, self is referred to as "mental self" (James, 1957), "narrative self "(Gallagher, 2000), or "autonoetic consciousness" (Keenan, Wheeler, Gallup, & Pascual-Leone, 2000), which involves higher-order cognitive mechanisms linking them to consciousness. Experimentally, this "self-referential self" is usually analyzed by presenting stimuli such as words or faces that the subjects are asked to evaluate according to their degree of self-referentiality, i.e. being either self- or non-self specific. Thus, they represent predominantly an external point of view to oneself. These studies indicate the involvement of cortical midline structures, specifically medial prefrontal, anterior cingulate, precuneus and posterior cingulate areas of the brain during processing of self-specific stimuli when compared to non-self-specific ones (Han & Northoff, 2009; Northoff et al., 2006).

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Alternatively, another concept of the self has been advocated, which focuses not on higher-order cognitive but rather on basic somatic and affective functions, thus, relating more to an internal point of view of oneself. This lower-order concept of self refers to a "corporeal self" (Pribram, 1999), a "proto-self" (Panksepp, 1998), or a "material me" (Craig, 2003), and is associated with "self-related" rather than self-referential processing (Northoff et al., 2006; Northoff, Qin, & Nakao, 2010). Experimentally, this concept is tested while presenting self-specific stimuli like the own name which are distinguished from non-self-related stimuli like the names of others (see for instance Qin et al., 2010). Interestingly, these studies have also indicated that cortical midline structures are activated upon self-specific stimuli presentation (Northoff et al., 2009; Qin et al., 2010). The following concept of the self is also empirically supported by findings demonstrating the division between affective and cognitive components of the self (Moran, Heatherton, & Kelley, 2009; Moran, Macrae, Heatherton, Wyland, & Kelly, 2006) and subcortical areas (Northoff et al., 2009; Schneider et al., 2008) in the processing of self-related stimuli. Thus, sufficient empirical evidence appears to support a conceptual distinction between lower- and higher-order concepts of the self.

Alongside this distinction, recent evidence indicates a substantial structural overlap between neural regions involved in the self processing and those regions which characterize the resting state modes (D'Argembeau et al., 2005; Northoff et al., 2006; Qin et al., 2010; Schneider et al., 2008). However there is a lack of evidence how these internally-oriented stimuli with a high-degree of self-relatedness are linked to external stimuli with different degree of self-relatedness. To date, only few studies specified the interconnection between self and other perception. Thus, Kjaer, Nowak, and Lou (2002) using stimuli in the reflection of the own personality traits and own physical appearance in comparison with reflection of personality and physical appearance of the other reported the connectivity by the synchrony between ACC and precuneus.

In the present study we aim to investigate the neural correlates of the perception of stimuli, which are suspected to be self-related and self-referential without involving an explicit evaluation or judgment. We located a paradigmatic case in the taxonomy of single case studies (Flyvbjerg, 2006), an eminent opera-singer with a prominent professional identity in order to test the following hypotheses: (1) Are cortical midline structures involved in the processing of self-specific stimuli and (2) is there a difference between processing of self-referential and self-related stimuli in the brain? The unique case allowed us to apply both types of stimuli: self-related (listening to the own voice and singing by inner voice) and self-referential (listening of music and listening to the same piece sang by another singer) in fMRI design assuming that cortical midline structures might be differentially recruited in these tasks.

2. Methods

2.1. Participant

A right-handed (Edinburgh Handedness Inventory) person (female, age = 69 years) in good general health and with no history of neurological or psychiatric illness participated in the study. The subject has been professional soprano singer for more than 35 years and currently is a professor of singing. Written informed consent to participate was gained prior to the study, and the subject was informed of her right to discontinue participation at any time. The study was carried out in accordance to the Declaration of Helsinki principles and was approved by the ethics committee of the Medical Faculty of the University of Munich.

2.2. Stimuli and task

Four experimental conditions were used in the study: (1) listening to short excerpts from recordings of the subject's own singing – *LS*; (2) listening to recordings of the same musical pieces sung by another person – *LO*; (3) listening to instrumental music without vocal part - *LM*; and (4) active inner (not audible) singing accompanied by instrumental music, a task for which professional singers are well trained – *SM*; The stimuli consisted of digitalized music, *coloratura* excerpts of two Mozart arias of 15–20 s duration: (1) Magic Flute: "Der Hölle Rache kocht in meinem Herzen" (Königin der Nacht, II); (2) Don Giovanni: "Crudele?" – "Non mi dir, bel' idol mio" (Donna Anna, II). These excerpts were representative for the repertoire sung by the subject during her professional career. All stimuli were normalized in loudness.

Stimuli were presented under computer control binaurally in pneumatic headphones at a sound level comfortable to the subject. Headphones also served to alleviate the noise of the scanner. The subject was asked to keep her eyes closed during the whole experiment and the light was dimmed to suppress visual stimulation.

The study was conducted in four test sessions (runs). As perception of music requires cognitive integration over time, the experimental paradigm was based on the classical block-design: during each run the four conditions (*LS, LO, LM,* and *SM*) were presented four times each, in *random order*. At the beginning of each run an additional short (3 s) dummy recording (coloratura excerpt from Mozart's Die Entführung aus dem Serail: "Martern aller Arten", II/3) was presented to avoid startling of the subject and prepare her for the testing period. The subject was instructed to attentively listen to the musical stimuli for the conditions *LS*, *LO* and *LM* or to sing with inner voice (inaudibly) in the condition *SM*. The last task is habitual for professional singers and is typically used to prepare for performances. For the condition *SM* the same instrumental music as in the condition *LM*, preceded by a short recorded instruction (female voice, 3.5 s before each start of the condition *SM*) was used. Between conditions, a silence period was provided for 6, 9, 12 or 15 s – in random order (*Baseline*). The functional measurement session lasted approximately 45 min in total.

2.3. Data acquisition

Experiments were conducted on a 3 T whole body system (Magnetom VERIO, Siemens, Erlangen, Germany), equipped with a standard head coil. The subject's head was securely but comfortably fastened by foam cushioning in order to minimize head movements. For blood oxygen level dependent (BOLD) functional imaging, an T2*-weighted Echo-Planar Imaging (EPI) sequence was used with the following parameters: repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, number of slices = 28, slice thickness = 4 mm, inter-slice gap = 0.4 mm, interleaved acquisition, field of view (FoV) = 192 × 192 mm, matrix = 64 × 64, in-plane resolution = 3 × 3 mm. Functional images were acquired in axial orientation, covering the whole cerebrum and dorsal cerebellum.

2.4. Data analysis

Data was analyzed with SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). The first five volumes were discarded due to T1 saturation effects. All functional images were realigned, spatially normalized into standard stereotaxic space (EPI template; Montreal Neurologic Institute, MNI), resliced to 2 × 2 × 2 mm voxels, and smoothed with an 8 mm full-width at half maximum (FWHM) Gaussian kernel. Statistical parametric maps were thresholded at $p < .001$ (cluster-level FWE corrected at $p < .001$, cluster size threshold = 400 voxels). Anatomical

description was done referring to the AAL atlas (Automated Anatomical Labelling of Activations; Tzourio-Mazoyer et al., 2002) from the MRIcroN (http://www.sph.sc.edu/comd/rorden/mricron). Internal reliability of the results was confirmed by conducting independent analysis for each music excerpt.

3. Results

The initial comparisons of task-related conditions and baseline were performed sequentially for passive conditions of listening (*LS, LO*) and active singing of music (*SM*). Several areas, specifically bilateral temporal cortex and anterior temporal gyrus, sensorimotor, premotor areas exhibited significant increase of BOLD signal during listening to self and other conditions in comparison to the baseline. In active condition (*SM*) versus baseline there has been an increase of BOLD signal in sensorimotor, premotor, prefrontal areas and cerebellum, and to the lesser extends in right and left temporal regions.

To define brain areas particularly involved in the processing of *self* versus *others*, we have conducted several pair-wise comparisons between experimental conditions (Table 1). *LM* served as a control condition in order to show specific neural activations occurring in both *LS* and *LO* conditions. The comparison between listening self and listening music (*LS* > *LM*) revealed bilateral activation in the dorsolateral and medial prefrontal cortex, anterior cingulate cortex, which constitute the biggest cluster of activation in the brain, as well as angular and middle occipital gyri. We also observed activation of the left orbitofrontal cortex with extension into superior frontal gyrus. Similar activation of MPFC and ACC was obtained in comparison of listening to others and listening music conditions (*LO* > *LM*).

The cerebral areas which share common activation in processing of *LS* and *LO* were chosen for conjunction analysis between the following contrasts: *LS* vs *LM* and *LO* vs *LM*. Mutual activation was detected in bilateral dorsomedial prefrontal cortex (DMPFC) and right anterior cingulate (ACC) (Fig. 1A). In the direct comparison of listening to *self* vs *others* (*LS* > *LO*), we observed a relative increase of the BOLD signal in – left thalamus, cerebellum, right-lateralized cuneus and precuneus (Fig. 1B).

Comparison between active singing and listening showed no difference in activation singing music vs. listening self (*SM* > *LS*), as well as singing music vs. listening music (*SM* > *LM*) conditions (Table 1). No activations were obtained between singing music and listening to other condition (*SM* > *LO*). Conjunction analysis between listening to self/singing self vs. listerning to the other contrasts (SM vs LO) and (LS vs LO) showed common activation in bilateral precuneus and superior temporal guri.

4. Discussion

In the present study we aimed to identify the brain structures involved in self-referential and self-related reflective activity being aware of the difficulties interpreting such observations (Bao & Pöppel, 2012). By applying a single case design we elude inter-subject heterogeneity of group studies and focus on complexities arising from the distinctive history and epigenetic influences specific to that individual. The sound of the own voice shapes social identity of a professional opera singer; in this particular case her personal identity is influenced by her professional specialization. We consider an eminent singer who possesses strong long-lasting professional experience and social identity to be a good example how to demonstrate interconnections of self-oriented processes.

As our main finding, the direct comparison between listening to *self* and *others* has showed a relative activation of precuneus, visual cortex, posteriolateral thalamus, and cerebellum in the perception of *self*. In addition, tasks that involve the *self* processing showed common activation of the precuneus indicating its specific role in self-related processing (Whitfield-Gabrieli et al., 2011). Subcortical structures have been previously considered as crucial subcomponents of functional systems for sensory integration (Tyll, Budinger, & Noesselt, 2011). The metabolic activity in subcortical brain areas and cerebellum has been also shown to be increased in mental processing (Decety, Sjoholm, Ryding, Stenberg, & Ingvar, 1990) and it could be involved in the regulation of the affective reactions and in forming the association between sensory stimuli and their emotional values (Strata, Scelfo, & Sacchetti, 2011). Visual cortex activation may indicate visual imagery (D'Esposito et al., 1997) and/or retrieval from autobiographic memory (Svoboda, McKinnon, & Levine, 2006). Overall, the findings might be an indication for the existence of a more basic, lower-order processing of self in terms of bodily functions and their sensory integration in the constituting of self-relatedness and identity. The derived clusters of neural activations might be a key distinction between the processing of *self* and *others*. One can also assume that self-related conditions might just elicit more memories resulting in more brain activations, therefore capturing also a quantitative (more memories = more effort/more processes) difference between self-related and self-referential processing.

Table 1
Neurofunctional correlates.

	Cluster	kE	Peaks				Brain area
			x	*y*	*z*	*Z*-value	
Passive conditions comparisons							
LS > LM	1	3637	−28	58	2	6.41	L. superior frontal g., middle frontal g., inferior frontal g., cingulate g., R. superior frontal g., middle frontal g., inferior frontal g., cingulate g.
	2	184	−36	−62	36	5.07	L. angular g., middle occipital g.
LO > LM	1	1145	8	46	20	5.23	L. superior frontal g., R. superior frontal g., cingulate g.
(LS > LM) ∩ (LO > LM)	1	1141	6	46	22	5.11	L. superior frontal g., R. superior frontal g., cingulate g.
(LS > LO) ∩ (SM > LO)	1	514	−16	−56	−22	4.29	L. cerebellum, R. cerebellum
	2	449	−12	−76	60	4.23	L. precuneus, cuneus, R. precuneus
LS > LO	1	589	0	−64	−24	5.23	L. cerebellum, R. cerebellum
	2	184	−24	−16	26	4.48	L. thalamus
	3	329	−2	−84	36	4.37	L. precuneus, cuneus
Active conditions comparison							
SM > LO	1	389	−14	−72	64	5.51	L. precuneus, superior parietal g.,
R. precuneus, superior parietal g.							

LS = listerning to self, LM = listerning to the music, LO = listerning to the other, SM = singing music, ∩ = conjunction. R. = right, L. = left, g. = gyrus. The *x*, *y* and *z* coordinates are in the MNI space.

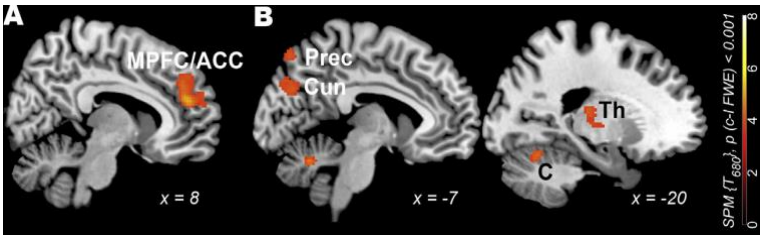

Fig. 1. Neurofunctional correlates of Self and Other processing. (A) Conjunction of *self* vs *music* and other vs Music processing: *DMPFC* = dorsomedial prefrontal cortex, *ACC* = anterior cingulate cortex; (B) Self versus Other processing: *P* = precuneus; *Th* = thalamus; *C* = cerebellum. Statistical parametric maps ($p < .001$, FWE cluster-level corrected). *X* coordinates are MNI coordinates.

In listening to *self* versus listening to *music* contrast, higher activation in predominantly dorsomedial PFC/ACC and orbitofrontal cortex (OFC) was detected. These regions are associated with the "first person" perspective and mental state's attributions (Vogeley et al., 2004) as well as its generally implicated in planning cognitive behavior, personality expression, decision making and error monitoring (Carter et al., 1998; Miller, Freedman, & Wallis, 2002). Moreover, the increased activity of angular gyrus, which was also reported, has been seen in experienced singers and which has also attributed to the action awareness and referred to the processing and comparison of action intentions and action consequences (Farrer et al., 2008). At the same time, listening to *others* versus listening to *music* has similarly shown the involvement of MPFC/ACC. Our results are consistent with the notion that above mentioned higher-order cognitive functions might facilitate the discrimination of self-referential stimuli from the context.

In summary, our findings corroborate the hypothesis of the specific modulation of the neural activity in cortical midline structures (CMS) during *self* processing (Northoff & Bermpohl, 2004, Qin & Northoff, 2011). Nevertheless, there has been a differentiation in activation with regard to self-related (lower-level) and self-referential (higher-level) processing. Firstly, activation in precuneus and subcortical structures proving the distinction between *self* and *others*, might sustain the sensory integration of the stimuli to the personally related context i.e. emotional and autobiographical and hence, comply with the lower-order functions. Secondly, perception of *self* and perception of *others* in reference to self produce common pattern of activation of MPFC and ACC with additional activation of OFC in perception of the *self*. Regarding the specific role of each of the region, one can argue that OFC seems to elucidate continuous representation of self-referential stimuli, it also explains why OFC is not activated in listening to other's condition. Once the self-referential stimulus is represented it appears to be evaluated in the MPFC and monitored for the performance in the ACC. In a word, the actual self-referential processes are obviously embodied by higher-order cognitive functions. Experimentally, the lower- and higher-order concepts of the *self* can also be distinguished with respect to its active or passive involvement. The higher-order *self* is conceived of as an "active *self*" in a sense that it requires evaluation and judgment and hence explicit conscious awareness. The lower-order *self* is considered as more passive as it does not require active involvement or an explicit representation of selfness and is therefore presumably related to sensory and motor functions or in general to more bodily functions rather than to cognitive processes and considered as internally-oriented self-relatedness (see for instance Grimm et al., 2009; Northoff et al., 2009; Schneider et al., 2008). A further distinction has to be made with respect to the time domain of the different *self* concepts (Pöppel, 2009, 2010; Pöppel & Bao, 2014). Whereas the higher-order *self* possibly represents a long-term perspective as reference is made to stable features of the *self*, the lower-order *self* is characterized by experiential references which are typically embedded in a shorter time window. This notion might be an interesting target for future research on the *self*.

Our study also showed that activation patterns in active *singing* with inner voice vs listening to *music* as well as active singing vs listening to self didn't differ that is probably due to involuntary silent singing even without an explicit instruction).

5. Conclusions

The present case study is a demonstration of the interconnection and interplay of corresponding neural modules involved in self-related and self-referential processing. These components of *self* should not be understood as independent identities but rather as the elements and working of complex networks. Higher-order cognitive concepts of oneself, connected to personal memories, feelings, and specific mental states which allow a re-experiencing of one's individual history (Gallagher, 2000) and location of oneself in subjective time (Pöppel, 2009; Pöppel & Bao, 2014), are presumably complemented by lower-order implicit states of a phenomenological pre-reflective self-awareness (Zahavi, 2007), which lack for instance subjective time extension (Strawson, 2002).

In most studies on the neural representation of the *self*, verbal stimuli are used and they trigger an explicit representation with semantic connotations. Our results provide an argument for representation of another sensory channel resulting in a more implicit neuronal information processing and knowledge representation (Pöppel & Bao, 2011) similarly allow uncovering various aspects of the *self* on a neural level. We found differences in neural activity for *self* and *other* perception in the cortical midline structures and subcortical regions. The fact that such differences were indeed observed suggests that musical stimuli can also represent specific aspects of self-relevant sensory inputs.

Conflict of Interest

The authors declare that they have no conflict of interest regarding this study.

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3. Summary of paper II

In the second part of this thesis, published by Park et al. (2015), the effects of ‘’musical training on the neural processing of emotions’’ conveyed in speech prosody were investigated. Musical training has been found to influence the neural processing of music, likely due to structural and functional brain changes in the musicians, influencing their professional identity. In the experiment, ‘’both musicians and non-musicians listened to sentences with three different emotional intonations communicating happiness, sadness, and fear, as well as neutral sentences spoken with a neutral intonation’’, as part of an fMRI task-related study. The findings revealed that musicians' emotional processing was more sensitive to grief portrayed in speech. On a neurological level, musicians showed increased activation in sections of the default mode network (DMN) in the middle frontal gyrus of the dorsolateral prefrontal cortex. The DMN has been linked to emotion induction, self-processing, affective saliency, and social processing, including attributing mental states to self and others.

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Sadness is unique: neural processing of emotions in speech prosody in musicians and non-musicians

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Musical training has been shown to have positive effects on several aspects of speech processing, however, the effects of musical training on the neural processing of speech prosody conveying distinct emotions are yet to be better understood. We used functional magnetic resonance imaging (fMRI) to investigate whether the neural responses to speech prosody conveying happiness, sadness, and fear differ between musicians and non-musicians. Differences in processing of emotional speech prosody between the two groups were only observed when sadness was expressed. Musicians showed increased activation in the middle frontal gyrus, the anterior medial prefrontal cortex, the posterior cingulate cortex and the retrosplenial cortex. Our results suggest an increased sensitivity of emotional processing in musicians with respect to sadness expressed in speech, possibly reflecting empathic processes.

Keywords: functional magnetic resonance imaging, language processing, prosody, basic emotions, musical training, temporal processing

INTRODUCTION

Musical training is associated with changes in cognitive and affective processing (Barrett et al., 2013). Musicians exhibit different expressions of musical emotion (Juslin and Laukka, 2003), and show stronger emotional experience in response to music (Blood and Zatorre, 2001). Musicians possess higher skills for the recognition of emotions expressed in music (e.g., Bhatara et al., 2011), and they differ from non-musicians in the processing of the sadness and fear conveyed in music (Park et al., 2014). However, the effects of musical training are not limited to the musical domain, and in particular certain aspects of speech processing have been shown to benefit from musical training (Thompson et al., 2004; Hyde et al., 2009; Lima and Castro, 2011; Patel, 2011, 2014). Musicians show improved performance in the encoding of speech sounds (Musacchia et al., 2007; Wong et al., 2007; Strait et al., 2009a,b), in detecting speech in noise (Strait and Kraus, 2011a), in extracting rhythmical patterns in auditory sequences (Su and Pöppel, 2012), and in processing pitch in speech (Moreno and Besson, 2005; Magne et al., 2006; Besson et al., 2007; Musacchia et al., 2007; Chandrasekaran and Kraus, 2010). Moreover, musicians seem to possess advantages in processing speech prosody (Thompson et al., 2004; Lima and Castro, 2011) and extra-linguistic properties such as the emotional content of speech (Nilsonne and Sundberg, 1985; Schön et al., 2004; Chartrand and Belin, 2006; Magne et al., 2006).

The advantages musicians exhibit in both music and speech processing have been explained by enhanced acoustic skills that musicians acquire through continuous training (Patel, 2003; Chartrand et al., 2008). The transfer effect from musical training to speech processing is assumed to be due to acoustic and rhythmic similarities between the two functional domains (Besson et al., 2011; Strait and Kraus, 2011b; Jäncke, 2012). Specifically in the communication of affect, music and speech share strong similarities, which has motivated the proposition of a shared "emotional protolanguage" of music and speech (Thompson et al., 2012). In order to express emotions, both music and speech make use of the same or similar acoustic elements such as timbre or pitch (Patel, 2003; Besson et al., 2007; Chartrand et al., 2008). Similarities between music and speech are also observed in the temporal domain as musical and verbal expressions use "temporal windows" of a few seconds within which musical motives or speech utterances are represented (Pöppel, 1989, 2009).

These strong associations between music and speech have also been observed on the neural level. Similarities have been found in brain networks active during processing of both music and language (Maess et al., 2001; Levitin and Menon, 2003; Brown

et al., 2004; Koelsch et al., 2004; Abrams et al., 2011; Zatorre and Schönwiesner, 2011; Escoffier et al., 2013; Frühholz et al., 2014), and it has been assumed that the communication of emotion in both domains may be based on the same neural systems associated with social cognition, including the medial superior frontal gyrus (SFG) and the anterior cingulate cortex (ACC; Escoffier et al., 2013). Similar to music, processing of emotional speech prosody has traditionally been associated with right hemispheric activation (Schirmer and Kotz, 2006; Wildgruber et al., 2006) but this view has recently been challenged by multi-phase models that assume several stages to be involved in emotional prosody processing recruiting both the left and the right hemisphere (e.g., Brück et al., 2011; Kotz and Paulmann, 2011; Witteman et al., 2012; Grandjean and Frühholz, 2013; Kotz et al., 2013). The network of brain areas involved in processing emotional prosody is assumed to mainly consist of the primary auditory cortices, the superior temporal gyrus (STG) and the inferior frontal gyrus, as well as subcortical regions including the amygdala and the hippocampus (Ethofer et al., 2012; Frühholz et al., 2012, 2014; Frühholz and Grandjean, 2013a; Kotz et al., 2013; Belyk and Brown, 2014).

Music training has been shown to alter the neural processing of music presumably based on functional and structural changes in the musician's brain (Hyde et al., 2009; Kraus and Chandrasekaran, 2010). Are the transfer effects of musical training on speech prosody processing also observable on the neural level? Research has been supportive of this view and it has been suggested (Besson et al., 2011; Strait and Kraus, 2011b; Patel, 2014) that intense and continuing musical training leads to structural and functional changes of the brain that advance cognitive processes and increases sensitivity to acoustic features in music processing (Besson et al., 2011; Strait and Kraus, 2011b) which may subsequently also improve speech and specifically prosody processing. A number of studies have described differences between musicians and non-musicians in speech and prosody processing on the neural level (see Wong et al., 2007; Strait et al., 2009a,b; Patel, 2014). However, these studies have investigated the advantages in musicians compared to non-musicians on the level of subcortical auditory processing (Kraus and Chandrasekaran, 2010). To our knowledge, no brain imaging study has to date explicitly investigated the effects of musical training on cortical activation patterns in response to emotions conveyed in speech prosody. In line with previous studies showing that individual differences, such as stable personality traits, and also acquired musical expertise (Park et al., 2013, 2014), alter the neural responses to musically conveyed emotions such as sadness and fear, we aimed at identifying a potential cross-modal effect of musical training on the neural processing of speech prosody conveying different emotions. We expected musical training to be associated with an enhanced competence of emotional recognition, and distinctive differences in neural responses to emotional speech prosody.

METHODS

PARTICIPANTS

Twenty four healthy volunteers participated in the study. Twelve were non-musicians (7 female, mean age = 19.00, SD = 0.60) who had no previous musical training and did not play any instruments, and 12 were musicians (7 female, mean age = 20.25, SD = 1.76 years) who had received formal music training (mean years of training = 13.83, SD = 2.58 years) in a variety of musical instruments (stringed instruments: 29%, accordion: 24%, piano: 35%, flute 12%). All participants were right-handed. All of them were German native speakers. None of them had a record of neurological or psychiatric illness, head trauma or psychoactive substance abuse, or had contraindications for MRI (e.g., pacemaker implant, pregnancy). Musicians and non-musicians did not differ in general health (GHQ-12, German Version by Linden et al., 1996), (independent t-test: $t_{(21)} = 1.88$, $p > 0.05$) or general intelligence ($t_{(22)} = -0.65$, $p > 0.05$). There was no difference between the groups in mood, measured by the "Delighted-Terrible Scale" (Andrews and Withey, 1976), before (Mann-Whitney U-test: $z = 1.17$, $p > 0.05$), or after the experiment ($z = -0.06$, $p > 0.05$), also there was no differences within neither the non-musician (Mann-Whitney U-test: $z = 0.46$, $p > 0.05$) nor the musician ($z = 1.38$, $p > 0.05$) group before and after the experiment. The study was performed in accordance to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the ethics committee of the Medical Faculty of the University of Munich. All participants signed an informed consent.

MATERIAL

Items from the Berlin Database of Emotional Speech (Burkhardt et al., 2005) were used for the study. The database includes pre-evaluated semantically neutral sentences spoken in German in six different emotional tones (happiness, sadness, fear, disgust, boredom, neutral) by five different male and female actors. For the present study, sentences spoken by both male and female voices with three different emotional intonations conveying happiness, sadness and fear were selected. Neutral sentences spoken with a neutral intonation served as the control condition. The stimuli set has been evaluated for correct identification rates and naturalness of expression (Burkhardt et al., 2005) and for the present study, only stimuli with high values for correct detection (>65%) and naturalness (>65%) were chosen. To provide comparable and relatively long duration times, several original recordings of a given emotional quality by the same speaker were combined to last about 21 s each.

EXPERIMENTAL PROCEDURE

During scanning, participants listened to the stimuli binaurally via pneumatic, noise attenuating and non-magnetic headphones. Sound level was individually adjusted to be comfortable, and light was dimmed to suppress further visual stimulation. The participants listened passively to the sentences and were asked to keep their eyes closed during the experiment.

During three measurement sessions (runs) three emotional qualities (happiness, sadness, fear) and a control condition (neutral) were presented twice (same sentences and same emotional intonation but spoken by a female and a male speaker respectively). In total, six iterations (trials) of each emotion were presented. The different conditions were presented under computer control in a pseudo-randomized order. To control for order

effects, two versions of stimuli sequences were created and participants were randomly assigned to either one of them. Each stimulation-interval was followed by a pause. After scanning, participants listened to the set of stimuli again and were asked to identify the expressed emotion after each sentence by selecting an emotion from a provided list (happiness, fear, anger, disgust, sadness, surprise, neutral) or by choosing an individual label.

IMAGE ACQUISITION AND fMRI DATA ANALYSES

The experimental set-up was similar to a previous study (Park et al., 2014). MRI was performed using a 3 T whole body system (Magnetom VERIO, Siemens, Erlangen, Germany) at the University Hospital of the LMU Munich. The scanner was equipped with a standard TIM head coil (12 elements) and the participant's head was securely but comfortably fastened by a foam cushions in order to minimize head movements. For acquiring the blood oxygen level dependent (BOLD) functional images, an T2*-weighted Echo-Planar Imaging (EPI) sequence was used with the following parameters: repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, number of slices = 28, slice thickness = 4 mm, inter-slice gap = 0.4 mm, interleaved acquisition, field of view (FOV) = 192 × 192 mm, matrix = 64 × 64, in-plane resolution = 3 × 3 mm. Functional images were obtained in axial orientation, covering the whole cerebrum and dorsal cerebellum. A total of 183 scans were conducted for each participant over all three runs. The functional measurement session lasted approximately 10 min in total. To provide an anatomical reference and to rule out structural abnormalities, a sagittal high-resolution 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was performed: TR = 2400 ms, TE = 3.06 ms, FA = 9°, number of slices = 160, FOV = 240 × 256 mm, spatial resolution = 1 mm.

Data were analyzed with SPM8 (Statistical Parametric Mapping[1]). The first five volumes were discarded due to T1 saturation effects. All functional images were realigned ("estimate and reslice"), co-registered ("estimate"; EPI template; Montreal Neurologic Institute, MNI), spatially normalized ("estimate and write") into standard stereotaxic space using standard SPM8 parameters, re-sliced to 2 × 2 × 2 mm voxels, and smoothed with an [8 8 8] mm full-width at half maximum (FWHM) Gaussian kernel. Each condition was modeled by a boxcar function convolved with the canonical hemodynamic response function. At the first level, *t*-tests were computed for each subject and for each condition vs. the baseline. The baseline of statistical parametric maps in our study is comprised of time periods not defined as conditions in the first-level model (i.e., happy, sad, fearful, and neutral prosody). The individual contrast images for each subject were used for the random-effects second level analysis (Full factorial design with one between-subjects (musicians, non-musicians) and one within-subjects (happy, sad, fearful, neutral prosody) factors). The statistical parametric maps were cluster-level thresholded (cluster-level thresholded at p(FDR) < 0.05, starting from p uncorrected < 0.01; cluster-size threshold = 300 voxels). Anatomical description was done referring to the AAL atlas (Automated Anatomical Labeling of Activations; Tzourio-Mazoyer et al., 2002).

[1]http://www.fil.ion.ucl.ac.uk/spm

RESULTS

IDENTIFICATION TASK

A main effect of emotion was revealed by a two-way analysis of variance (ANOVA) with *emotion* as within-subject variable and *group* as between-subject variable, $F_{(3,66)} = 9.454$, $P < 0.001$. Further paired *t*-tests showed that sadness conveyed by speech prosody was as easily identified as neutral voice (0.69 vs. 0.70 in correct identification rate, $P > 0.05$), while happy and fearful voices were equally difficult to be identified (0.48 vs. 0.58 in correct identification rate, $P > 0.05$), as significant differences were only observed between the two categories (i.e., sadness and neutral vs. happy and fear, $P < 0.05$). Importantly, no significant main effect of *group* was observed, $F_{(1,22)} = 1.546$, $p > 0.05$, and no significant two-way interaction was observed either, $F_{(3,66)} = 1.728$, $p > 0.05$. These results seemed to indicate that both musicians and non-musicians are equally capable to identify emotions conveyed in speech prosody, although both groups are better at recognizing sadness as compared to fearful and happy emotions.

SIMILARITIES BETWEEN GROUPS—CONJUNCTION ANALYSIS

Conjunction analysis (conj. null) for the three basic emotions (happiness, sadness, fear) vs. baseline revealed bilateral activation in the temporal cortex, specifically in middle temporal (BA 21) and STG (BA 22) (**Table 1**, **Figure 1**). Possibly due to scanner noises, no distinct increases of activation were found in primary auditory cortices in response to the three emotions.

DIFFERENCES BETWEEN GROUPS

We observed significant differences in neural activation between the groups in response to sentences with sad prosody. In response to sad prosody musicians showed a significant increase of activation in the frontal cortex (BA 10, BA 9, 46), ACC (BA 32), posterior cingulate (BA 23, 31) and retrosplenial cortex (BA 29, 30) (**Table 1**, **Figure 2**). We did not observe any differences in neural activation between musicians and non-musicians in response to happy or fearful prosody. No increases of activation for non-musicians relative to musicians in response to any of the emotions were found.

DISCUSSION

The present study revealed similarities and differences between musicians and non-musicians in processing of emotional speech prosody expressing happiness, sadness and fear.

Conjunction analysis for fear, happiness and sadness revealed bilateral activations in temporal cortex, in the middle temporal gyrus (MTG) and the STG in both musicians and non-musicians. These areas are part of an auditory processing stream for categorizing auditory information (Hickok and Poeppel, 2007), including the identification and processing of linguistic and paralinguistic features of speech (e.g., Wildgruber et al., 2005; Schirmer and Kotz, 2006; Ethofer et al., 2012). The STG and the MTG crucially involved in processing emotional prosody

Table 1 | Neurofunctional correlates.

Brain region	Cluster	kE	Coordinates			*Z*-value
			x	*y*	*z*	
A. Conjunction (all emotions vs. baseline)						
R. superior temporal g., R. middle temporal g. (BA 21, 22)	1	548	66	−10	−6	3.72
L. middle temporal g., L. superior temporal g. (BA 21, 22)	2	359	−64	−16	−2	3.37
B. Sadness (musicians vs. non-musicians)						
R./L. cingulate g., middle part, R./L. precuneus, R./L. cingulate g., posterior part (BA 23, 31, 7, 29, 30)	1	1591	2	−40	40	3.72
R./L. cingulate g., anterior part, R. middle frontal g., R. superior frontal g., R. superior frontal g., medial part (BA 9, 10, 46, 32)	2	962	12	44	8	3.64

Note. kE = size in voxels (2 × 2 × 2 mm). R. = right, L. = left, g. = gyrus. The x, y and z coordinates are in the MNI stereotactic space.

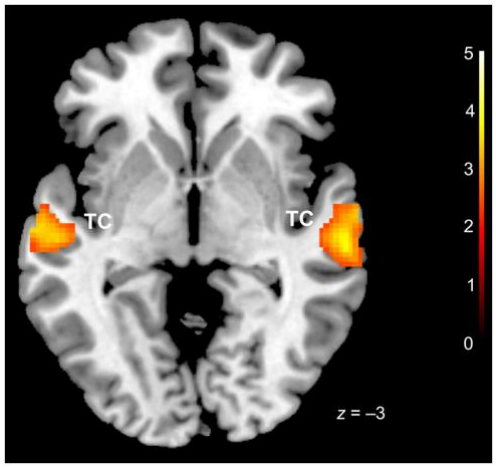

FIGURE 1 | Conjunction analysis (happiness, sadness, fear vs. baseline). TC = temporal cortex. *x* coordinate is in the MNI stereotactic space; cluster-level thresholded at *p* (FDR) < 0.05.

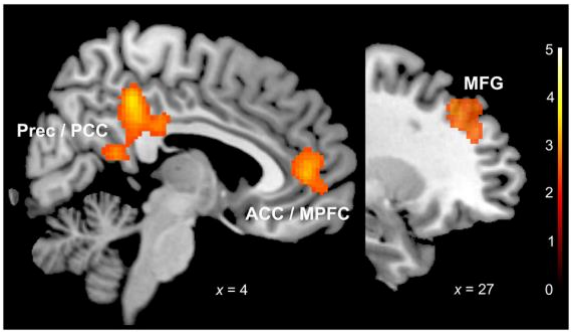

FIGURE 2 | Sadness (musicians vs. non-musicians). ACC: anterior cingulate cortex; MPFC: medial prefrontal cortex; MFG: middle frontal gyrus; Prec: precuneus; PCC: posterior cingulate cortex. *x* coordinate is in the MNI stereotactic space; cluster-level thresholded at *p* (FDR) < 0.05.

(e.g., Mitchell et al., 2003; Leitman et al., 2010; Frühholz and Grandjean, 2013b; Grandjean and Frühholz, 2013) and reliably, the (right) STG is found in studies on emotional prosody processing (Brück et al., 2011; Ethofer et al., 2012; Frühholz et al., 2012; Frühholz and Grandjean, 2013a; Kotz et al., 2013; Belyk and Brown, 2014). It is assumed to play a major role in the early stages of prosody processing and has recently been referred to as the crucial part of the "emotional voice area" (Ethofer et al., 2012).

These common activations suggest that in musicians and non-musicians similar neural mechanisms are recruited for early stage processing of emotional vocal stimuli.

Apart from these similarities we also observed differences in neural responses to emotional speech prosody between the groups. Specifically, musicians showed enhanced activations in several brain areas when responding to sentences spoken with sad prosody, suggesting higher sensitivity in emotion processing. Our observations will be discussed in the context of local neural activations and their assumed associations with subjective representations, being well aware of the conceptual problems when attributing high level cognitive processes to local neural modules or distributed neural networks (Bao and Pöppel, 2012).

We observed activation increases in the musician group in response to sad prosody in right frontal areas, in the middle and SFG (BA 10, BA 9, BA 46). Structural plasticity in right frontal regions has previously been associated with musical training (Hyde et al., 2009). Consistently, models on prosody processing agree in assuming the frontal cortex to play a crucial role in higher levels of prosody processing (see Witteman et al., 2012), specifically in the detection and judgment of emotional speech prosody (see Schirmer and Kotz, 2006). Specifically, the middle frontal gyrus has previously been found to be associated with processing of incongruity of in emotional prosody (Mitchell, 2013) and the detection of sad emotional tone (Buchanan et al., 2000). The stronger activations in right prefrontal areas may thus reflect processes related to the evaluation and categorization

of emotional prosody and it might also point to an enhanced sensitivity in the musician group specifically for the sad emotional content of the stimuli.

The increases in frontal activation for the group of musicians in response to sad speech prosody also included the an area comprising the medial part of the SFG and the ACC (BA 10, 32); areas that are both particularly associated with emotional processing, the appraisal and the regulation of emotions (Etkin et al., 2011), and also the induction of emotions (Amodio and Frith, 2006). The ACC is assumed to be part of a network specifically sensitive to monitoring of uncertainty and emotional saliency (Nomura et al., 2003; Cieslik et al., 2013) and the ACC and the medial prefrontal cortex have been specifically associated with the induction of sadness (Beauregard et al., 1998; Mayberg et al., 1999; Bush et al., 2000). Furthermore, the medial prefrontal cortex has been observed to be involved in emotional voice processing (Johnstone et al., 2006; Ethofer et al., 2012), and activation in the ACC has been found to play a special role in processing of emotional prosody (Bach et al., 2008; Belyk and Brown, 2014). We previously found increased activation in prefrontal regions in musicians in response to sadness in a study on musically conveyed emotions (Park et al., 2014) and Escoffier et al. (2013) found activations in the superior frontal cortex and the ACC during the processing of emotions that were expressed in music and through vocalization. The authors assumed that specific social processes might underlie emotion perception in both domains as both the superior frontal cortex and the ACC play a crucial role in mentalizing and other theory of mind (TOM) mechanisms (Escoffier et al., 2013). In fact, the medial prefrontal cortex and the ACC have consistently been associated with empathic processes and perspective taking (Amodio and Frith, 2006; Decety and Jackson, 2006; Etkin et al., 2011) and in particular the medial prefrontal cortex has been termed a "hub of a system mediating inferences about one's own and other individual's mental states" (Ochsner et al., 2004). The increased activations in the medial prefrontal cortex and the ACC in the group of musicians in response to sad sentences might thus suggest stronger emotional responses specifically related to the sad prosody of the stimuli. The increases of activation might furthermore point towards specific empathic processes related to the perceived sadness expressed in the stimuli (Harrison et al., 2007).

We also observed stronger activation in musicians in response to sad speech prosody in the posterior cingulate (PCC, BA 23, 31) and the retrosplenial cortex (BA 29, 30). The PCC and retrosplenial region have been associated with internally directed thought and episodic memory functions (Vann et al., 2009; Leech et al., 2012), and they are also involved in the "neural network correlates of consciousness", playing an important role in cognitive awareness, self-reflection (Vogt and Laureys, 2005) and control of arousal (Leech and Sharp, 2014). The PCC and retrosplenial region are also assumed to be involved in processing of the salience of emotional stimuli (Maddock, 1999) and the emotional content of external information (Cato et al., 2004), specifically of emotional words (Maddock et al., 2003). The increased activation we observed in the PCC and retrosplenial region in response to the sad prosody might, thus, reflect enhanced memory processes as well as increased assessment of emotional saliency of the sad prosodic stimuli and monitoring of arousal.

Some of the areas in which we found activation increases for musicians in response to sad speech prosody can be considered parts of the default mode network (DMN, Raichle et al., 2001; Buckner et al., 2008), specifically the cortical midline structures ACC and PCC and the anterior medial regions of the prefrontal cortex. The DMN shows strong activity at rest and deactivation during tasks that call for external attention. The DMN as a functional system has been associated with processing of self (Zaytseva et al., 2014) and reflects introspective activities and stimulus-independent thought. Such "mentalizing" detaches from the present moment in which stimulus processing takes place (Pöppel and Bao, 2014). Furthermore, the DMN has been associated with induction of emotions, processing of affective saliency (Andrews-Hanna et al., 2010) and with social-emotional processing (Schilbach et al., 2008, 2012), such as attributing mental states to self and others (e.g., Mars et al., 2012).

It may be a puzzling result that the only significant differences between the groups were observed in the neural response to prosody expressing sadness but not in response to the other emotions. However, sadness is consistently found to be one of the emotions that are easiest to recognize (see Thompson et al., 2004). It is characterized by a particularly relevance to social loss (Panksepp, 2005) and may therefore be considered a highly salient and socially relevant signal. Furthermore, the expression of sadness in both music and speech prosody relies on similar acoustic features (Curtis and Bharucha, 2010), which musicians, due to their enhanced acoustic skills, may be able to extract more readily. In a previous study on musical emotions (see Park et al., 2014), we also found that musicians showed stronger neural activations to musical excerpts conveying negative emotions including sadness, and indicated stronger arousal in response to sad music. It was hypothesized that musicians may possibly be at an advantage to respond to the high social saliency of this emotion due to certain gains in social-emotional sensibility. In fact, the social functions and effects of music making have recently received increased attention (Koelsch, 2013) and listening to music has been shown to automatically engage TOM processes such as mental state attributions (Steinbeis and Koelsch, 2009), possibly implying that musicians because of their ongoing training may be particularly experienced in those specific aspects of social-emotional cognition. In fact, there is some empirical indication that musical training does indeed positively influence social emotional and communication development (Gerry et al., 2012) and that musical interventions effectively improve social skills (Gooding, 2011). Thus, a specific increase of social competence and social-emotional sensibility may be one cross-functional benefit of long-term musical training. Assuming these potentially enhanced social cognitive and empathic competences, musicians might thus be more responsive to the high social saliency of sadness in speech prosody. However, while several studies have reported advantages in recognition of emotional speech prosody due to musical training (Thompson et al., 2004; Lima and Castro, 2011), we only observed the difference between musicians and non-musicians in identifying sadness on the neural level, but we did not find any significant differences on the behavioral level.

This dissociation between neural responses and verbal reports to sadness supports the general concept to distinguish between the levels of explicit and implicit experience (Pöppel and Bao, 2011). The fact that the difference between the groups was only observed on the neural level suggests that for musicians sadness may be characterized by a unique implicit representation. The neural activations we observed in response to the sad prosody, in particular the activations in the MPFC and other parts of the DMN (Ochsner et al., 2004; Mitchell et al., 2005; Amodio and Frith, 2006), may possibly reflect these social-emotional mechanisms that crucially involve implicit introspective, i.e., self-referential, processes to infer the mental state of the speaker.

Finally, while a transfer effect of musical training to speech processing may mainly depend on acoustic and rhythmic similarities between music and speech (see Jäncke, 2012) temporal mechanisms might constitute another driving force for this cross-functional learning effect. Temporal mechanisms are of utmost importance in coordinating cognitive processes and can be considered to be an anthropological universal (Bao and Pöppel, 2012). Positive learning effects related to temporal training have been observed previously on the level of temporal order thresholds (Bao et al., 2013) of native speaker of the tonal language Chinese who show different thresholds compared to subjects from a non-tonal language environment. Furthermore, temporal mechanisms are crucial for conveying poetry (Turner and Pöppel, 1988) and they can be regarded basic to the expression and experience of music (Pöppel, 1989). Since neuro-imaging studies have shown music and language to rely on similar neural structures (Abrams et al., 2011) and considering the temporal similarities between music and speech it might be suspected that musical training also positively impacts temporal processing, and the observed effects thus may reflect enhanced temporal sensitivity as an effect of inter-modal transfer (Pöppel, 1989, 2009) which might also involve a higher competence to detect sadness in speech.

In conclusion, consistent with a previous study showing differences in emotion processing presumably due to musical training (Park et al., 2014), our study supports the notion that such training also alters the neural processing of distinct emotions conveyed in speech prosody. In particular, while musicians and non-musicians do not differ in their performance in recognizing sadness in speech, they process this particular emotion significantly differently on the neural level. Musicians show distinct increases of neural activations only in response to the sad prosody, possibly due to a higher affective saliency that the sentences spoken with sad intonation might possess. Our results imply that the cross-modal transfer effects of musical training go beyond auditory processing and explicit emotional recognition skills; we suggest that such training may also impact the empathic aspects in human communication.

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4. Summary of paper III

It may also be argued in the third part of this thesis, published by Silveira et al. (2015), that religion and its contents constitute a basis for a sense of identity, especially among very religious people. Social identity theory posits the inclusion motive in human behavior and attitude. As a result, belonging to a religious group may give people a sense of self. Furthermore, religious belief has previously been claimed to affect self-referential processing on a neurological level. What role does religion have in influencing belief-related decisions and brain processing?

In a single case study, we used functional magnetic resonance imaging (fMRI) to infer about brain processing while a famous bishop of the Catholic Church in Germany was passively reading short lines from the Christian Bible, the Islamic Quran, and the Daodejing attributed to Laozi. ‘’Continuous praying was compared to resting state activities in a second trial’’. We found no difference in neural activation when the bishop read statements from the Bible and the Quran, in contrast to explicit statements of agreeing and disagreeing with different statements from the Bible and the Quran. However, ‘’reading statements from the Daodejing led to significantly higher activation in the left inferior and middle frontal cortices and the left middle temporal gyrus compared to the Bible’’. The functional connectivity of the brain during continuous praying and relaxing was not different in the second trial.

Our findings support the distinction between explicit and implicit processing, and they also show that a deeply religious individual prays either constantly or infrequently. This finding shows that ritualized behaviours may be done during the resting state on a more general level.

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Does a bishop pray when he prays? And does his brain distinguish between different religions?

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Abstract: Does a religion shape belief-related decisions and influence neural processing? We investigated an eminent bishop of the Catholic Church in Germany by using functional magnetic resonance imaging (fMRI) to assess neural processing while he was responding to short sentences of the Christian Bible, the Islamic Quran, and the Daodejing ascribed to Laozi in Experiment 1. In Experiment 2, continuous praying was further compared to the resting state activity. In contrast to explicit statements of agreeing or not agreeing to different statements from the Bible and the Quran, we found in Experiment 1 no difference in neural activation when the bishop was reading these statements from the two religions. However, compared to reading statements from the Bible, reading statements from the Daodejing resulted in significantly higher activation in the left inferior and middle frontal cortices and the left middle temporal gyrus, although he equally agreed to both statements explicitly. In Experiment 2, no difference during continuous praying and the resting state activity was observed. Our results confirm the difference between explicit and implicit processing, and they suggest that a highly religious person may pray always—or never. On a more general level this observation suggests that ritualized activities might be subliminally represented in resting state activities.

Keywords: brain connectivity; explicit judgment; fMRI; implicit knowledge; religious belief; resting state

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Single case studies have always been a source of insight and often raise new questions to be addressed (Flyvbjerg, 2006). With respect to religious belief and contemplation, the profession of a bishop warrants an intense engagement with religious content. It might even be argued that, especially in highly religious persons, religion and its contents form a basis for a sense of identity. Social identity theory (Tajfel & Turner, 1986) posits an inclusion motive inherent in human behavior and attitude. Being a part of a religious group might therefore provide people with identity (Pöppel, 2010). It has previously been suggested that even on a neural level, religious belief might modulate self-referential processing (Han et al., 2008).

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Throughout human history and across different cultures, religious belief has repeatedly been a source of prejudice, and has oftentimes motivated people to segregation or even war. Even after years of studying a brain-behavior relationship, it remains unclear whether these universal phenomena underlie specific neural patterns that might have evolved as a means to protect against potential threat as has been proposed for race-related prejudice (e.g., Chekroud, Everett, Bridge, & Hewstone, 2014). In studying a relationship between explicit and implicit levels of processing (Pöppel & Bao, 2011), functional magnetic resonance imaging (fMRI) is one of the most compelling technologies, measuring brain activation patterns while the subject is engaged in cognitive judgments.

Basic religious foundations are usually represented in written language, as religious tradition is mainly captured in scriptures. In a recent neuroimaging study employing religious statements as stimulus material, religious cognition has been found to engage brain networks associated with abstract semantic processing and theory of mind (Kapogiannis et al., 2009). In general, previous research has consistently demonstrated a stronger involvement of left hemispheric brain areas in reading tasks, with a reading network consisting of frontal, temporal, and parietal brain regions (Graves et al., 2014). In particular, phonologically based forms of reading have been associated with inferior frontal as well as superior and middle temporal activation (Joubert et al., 2004).

Some aspects of religious reasoning can be considered as universal, that is, being an inherent part of every religion, but every religious tradition is also characterized by cultural specifics. Thus, it might be expected that processing religious content of one's own compared to other cultures involves different neural, cognitive, and affective mechanisms. To obtain better insight into this question, we conducted a single case study using high-field magnetic resonance imaging to investigate in Experiment 1 neural and verbal responses to religious and non-religious statements; in Experiment 2 we compared resting state activity with continuous praying.

Experiment 1

Method

A German bishop aged 72 years who is an eminent representative of the Catholic Church in Germany participated in this experiment. His vision was corrected to normal. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee. Informed consent was provided. The stimuli in the first experiment were sentences from religious and non-religious literature. Stimuli were presented in the conditions "Christian Bible," "Islamic Quran," and "Chinese Daodejing." The Christian and Islamic conditions represented sentences from religious literature; the Daodejing as a classic Chinese text represented non-religious literature. All sentences were selected manually, matched in length, and they were presented in German translations. For each of the three conditions, eight different statements were selected to which the bishop had to respond by agreeing or not agreeing. Examples from the three conditions to which the bishop agreed were: Chinese Daodejing—"If you know your weakness, you maintain your strength"; Christian Bible—"Show me your way, God, that I can walk in your truth"; and Islamic Quran—"Think about the name of Allah in the morning and in the evening."

To measure the neural responses, we used a block design consisting of six blocks per condition. Each block contained three sentences as three stimuli. Each sentence was presented for 3700 ms, followed by 1000 ms displaying a question mark and 300 ms with a black screen. Between the blocks, the bishop viewed a black screen for 6 s. After the scanning session, the bishop was asked to orally evaluate whether or not he agreed or disagreed with the statements presented to him.

Functional MRI was performed using a 3.0-Tesla Magnetom (Ingenia, Philips Healthcare, Best, the Netherlands) with a 32-element head coil. For anatomical reference, a sagittal high-resolution 3D TFE sequence was acquired with the following imaging parameters: field-of-view (FoV): 230×230 mm; spatial resolution: $0.45 \times 0.45 \times 0.6$ mm; number of slices: 317; time of repetition (TR): 13.35 ms; time of echo (TE): 6.24 ms; and flip angle (FA): 8°. Functional data were recorded using a BOLD sensitive echo-planar gradient-echo sequence in axial orientation (FoV: 240×240 mm; spatial resolution: $3 \times 3 \times 3$ mm; number of slices: 53; TR: 3000 ms; TE: 30 ms; FA: 90°). Before starting imaging, 3D-field shimming was performed using automated shimming algorithms implemented on the scanner.

Statistical analysis was done by SPM 8 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm) and SPSS 19.0 (IBM, Armonk, NY, USA). Functional MRI data were changed from EPI DICOM to NIFTI by BrainVoyager 2.0.8 (BrainInnovations

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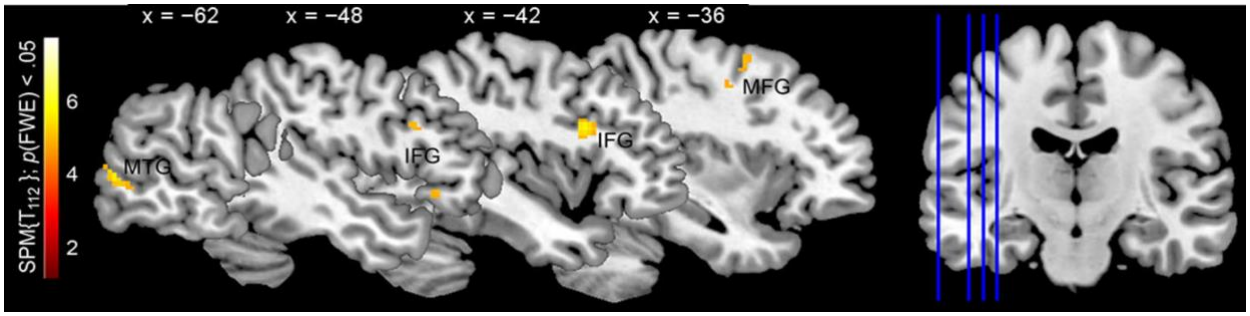

Figure 1. Statistical parametric mapping of processing religious sentences. Depicted activation differences are computed with *t*-statistics contrasting blood-oxygen-level-dependent signals when processing sentences of the Daodejing compared to sentences of the Bible. Activations are cluster-level corrected with *p* (familywise error; FWE) < .05. The x, y, and z coordinates are normalized using a standard brain from the Montreal Neurological Institute and displayed in radiological convention. Differential activation is presented in three sagittal slices within the left hemisphere. MTG = middle temporal gyrus; IFG = inferior frontal gyrus; MFG = middle frontal gyrus.

BV, the Netherlands). Functional data were motion corrected, aligned to the structural images, normalized (by use of a piecewise linear transformation model) into MNI space using the EPI template (Evans et al., 1993), resampled to 3 mm × 3 mm × 3 mm voxels and spatially smoothed to reduce noise using a Gaussian kernel of 8 mm full width at half maximum.

To specify first-level statistics, the conditions Christian Bible (Psalm), Islamic Quran (Sura) and Daodejing were compared to a default control condition that is implemented in the SPM software. Between-group comparison was done using *t*-tests. We used a familywise error corrected significance level of p (FWE) < .05. For further descriptive analysis, we extracted activation levels within four regions as defined by significant *t*-statistics of the single contrasts.

Results

On the behavioral level using a dichotomous scale, the bishop stated that he agreed to all statements from the Bible and the Daodejing, while he agreed to only three of the eight Islamic statements; this result is significantly different: $\chi^2 = 66.67$, $p < .001$. Neural activations for the Daodejing condition were significantly higher than for the Psalm condition in the left inferior frontal gyrus, middle frontal gyrus, and middle temporal gyrus (Figure 1; Table 1). The reverse contrast revealed no difference between the Daodejing and Psalm conditions. There was no significant difference between either the Psalm and the Sura conditions or the Daodejing and the Sura conditions.

When observing activation values that were extracted within those brain regions involved in the *t*-contrasts between conditions, we found that for the Daodejing condition, activation values were highest in every region, while for the Psalm and Quran conditions the values were rather low (Table 2).

Table 1

Neural Correlates of Religious Statements. Higher Activation for Sentences of the Daodejing Compared to the Psalm Condition

Brain region	Cluster size	Coordinates x	y	z	*z*-statistics
L inferior frontal gyrus Cluster 1	58	−42	14	24	5.37
L inferior frontal gyrus Cluster 2	14	−48	26	−6	4.75
L middle frontal gyrus	1	−36	4	56	4.77
L middle temporal gyrus	39	−62	−54	0	5.26

Note. Right (R) or left (L) hemisphere. The x, y and z peak coordinates are in MNI stereotactic space. *Z*-values of *t*-tests. p (familywise error) < .05.

Table 2

Mean Neural Activation Levels in Left Hemispheric Regions of Interest for the Three Experimental Conditions

	Inferior frontal Cluster 1	Inferior frontal Cluster 2	Middle frontal	Middle temporal
Daodejing	3.33	2.26	2.65	2.06
Psalm	−0.42	−0.19	−0.39	−0.26
Sura	1.99	0.72	2.05	1.04

Discussion

Our results illustrate an important dissociation of explicit and implicit responses to religious statements. Although the bishop indicated an explicit disapproval of sentences that were taken from the Quran, there was no significant difference between those sentences and the ones that were taken

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from the Christian Bible on the level of neurocognitive functioning. The preference for statements retrieved from the same religious context is, thus, not reflected in implicit neural processes. This indicates a dissociation of different pathways of mental processing, which highlights that disfavoring other religious contexts is not associated with implicit processes. This raises the question as to what the "real belief" actually is.

In contrast to the lack of any difference between neural responses to Biblical and Islamic statements, we found higher blood-oxygen-level-dependent signals in various brain areas when the bishop was reading statements from the Daodejing. In light of the concept of effortless processing (e.g., Bao & Pöppel, 2012), it could be argued that higher neural activation can be seen as indicative of a higher cognitive demand. Thus, speech-related processing when reading statements from the Daodejing might require more cognitive effort. This might especially be related to semantic aspects, as the Daodejing is characterized by abstract and paradoxical sentences. While it has previously been suggested that the processing of religious content itself engages abstract semantic processing (Kapogiannis et al., 2009), our observation indicates a higher involvement of brain areas, which in general respond to linguistic processing of written language, when processing the statements of the Daodejing. Thus, statements from the Daodejing representing aspects of Chinese tradition are apparently processed with higher effort due to the different cultural experience of the bishop.

Qualitatively, brain activation levels when reading literature from three cultures seem to follow a linear increase from processing statements out of the Bible to the Quran and finally to the Daodejing (see Table 2). This might reflect a gradual change of cognitive efforts with responses to the Quran condition residing in the middle. Even though the difference with either the Bible or the Daodejing condition was not robust enough to reach significance level in the statistical analysis with correction for multiple comparisons, the results do not allow for a conclusion as to whether statements out of the Quran are processed with a higher similarity to those out of the Bible or the Daodejing condition. However, our results indicate that the explicit disapproval of a different religious worldview, that is, statements from the Islamic Quran, is not reflected on the level of implicit neurocognitive processes. Only the reading of rather abstract and paradoxical statements that the bishop is not exposed to in the religious context of his own culture elicited a differential involvement of speech-related brain structures. The profession of a bishop might, however, influence brain activation patterns beyond phenomena separating the familiar from the unfamiliar. Religious expertise might decrease cognitive demands also in other domains of cognitive processing. Specifically, praying as a ritual of religious practice might be an effective means to modulate mental processes. To gain insight into potential effects of ritualized praying, we conducted Experiment 2 with the same subject.

Experiment 2

Spiritual rituals that can be related to contemplation, like religious prayers or meditation practices, have recently attracted neuroimaging research trying to explore neural correlates of a positive outcome of such practice on the well-being of people (e.g., Cahn & Polich, 2006; Davidson et al., 2003). Especially long-term practice in daily contemplation has been shown to modulate brain activation patterns (Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). Previous fMRI studies have yielded that meditation practice considerably influences resting-state functional connectivity in several brain networks (Froeliger et al., 2012; Taylor et al., 2013). In this sense, expertise in spiritual practice decisively alters brain activation patterns when the brain is at rest and not engaged in a specific task. Studies so far are, however, restricted to spiritual practices like Zen meditation. It still remains an open question as to how far these results apply also to religious praying. For an investigation of this question, we conducted Experiment 2 with the bishop, comparing the brain's functional connectivity during resting compared to praying the common catholic prayer "Our Father."

Method

For anatomical reference, the same sagittal high-resolution 3D TFE sequence was used as mentioned above (in Experiment 1). Functional data were recorded using a BOLD sensitive echo-planar gradient-echo sequence in axial orientation with the following parameters: FoV: 240 × 240 mm; spatial resolution: 3 × 3 × 3 mm; number of slices: 49; TR: 2500 ms; TE: 30 ms; flip angle: 90°; and number of volumes per scan: 240, resulting in a time of acquisition of 10:00 min for each scan (i.e., the resting-state and praying scan, respectively). For the resting-state scan, the bishop was instructed to keep his eyes closed without falling asleep and not to think of anything in particular. For the following scan, the bishop was asked to keep his eyes closed and to continuously pray in his mind the "Our Father" prayer.

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The data preprocessing steps were adapted to the procedure described by Biswal et al. (2010) using the software packages FSL (FMRIB Software Library, Oxford, UK), Release 5.0.7, and AFNI (Analyses of Functional NeuroImages, Bethesda, MD, USA) and included: (1) skull removing of the high-resolution T1-weighted image; (2) discarding the initial six volumes of each 4D functional dataset to account for T1 saturation effects followed by motion correction, skull stripping, spatial smoothing applying a 6-mm FWHM Gaussian kernel, grand-mean scaling, as well as removing of linear and quadratic trends of 4D functional datasets; (3) registration and normalization of anatomical and functional datasets to the MNI152 standard space applying linear and non-linear algorithms (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001); and (4) regression of the functional 4D datasets on signals derived from cerebrospinal fluid and white matter as well as on six motion parameters.

The preprocessed functional datasets derived from either condition—i.e., resting or praying—were separately decomposed into independent components (ICs) using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) software, version 3.14. The number of ICs was automatically estimated by MELODIC.

To be considered a functional connectivity network, the patterns shown in the ICs were required to extend over functionally relevant (i.e., cortical and subcortical) brain areas as reported in prior studies based on data-driven approaches (i.e., Independent Component analysis [ICA]; Beckmann, DeLuca, Devlin, & Smith, 2005; Beckmann & Smith, 2004; Biswal et al., 2010; Damoiseaux et al., 2006; Zuo et al., 2010) and to consist predominantly of signals in the frequency range between 0.01 and 0.1 Hz, which has been demonstrated to be characteristic for functional connectivity networks using BOLD fMRI (e.g., Cordes et al., 2001, Fox et al., 2005); patterns not meeting these criteria were considered artificial noise and removed from further analysis.

In order to enable the statistical comparison between the resting and the praying condition, the preprocessed fMRI data from both scans additionally underwent a combined evaluation using Temporal Concatenation Group ICA (TC-GICA) as implemented in FSL's MELODIC. In this case, the number of ICs was also automatically estimated. Among the resulting patterns, functional connectivity networks were extracted according to the same procedure as described above.

The TC-GICA-derived ICs containing functional connectivity networks were reconstructed into condition-specific ICs applying a dual regression approach. To test for between-condition differences, non-parametric testing as implemented in FSL's Randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) was applied to the condition-specific ICs. Due to the explorative nature of the single case study, we considered effects significant at a less conservative level of $p < .05$ (uncorrected for the number of voxels and networks).

Results

The separate MELODIC approaches yielded 13 ICs for the resting condition and 14 ICs for the praying condition; according to our criteria mentioned in the Method section, eight ICs of each condition were considered functional connectivity networks (Figure 2), while the remaining patterns were consistent with artificial noise (not described here). The eight networks—demonstrating a good overlap between conditions by visual inspection—are described as follows (note in that context that for the purpose of a better between-condition comparability, the order of networks found by MELODIC was adapted to that found in the resting condition). Network 1 demonstrated a connectivity pattern extending over the occipital cortex forming a visual network (Biswal et al., 2010). Network 2 combined the posterior parieto-temporal cortex extending into the lateral occipital cortex (Damoiseaux et al., 2006). The connectivity pattern in Network 3 included the precuneus, the posterior and anterior cingulate cortex, the ventromedial prefrontal cortex and the parieto-occipital junction; this pattern corresponds to the classic default-mode network (DMN; Raichle et al., 2001), which among others has been linked to theory of mind and social cognition tasks (Laird et al., 2011) and also has been shown to be influenced by meditation (Taylor et al., 2013); the connectivity pattern represented in Network 6 involved the medial prefrontal cortex and presumably constitutes an anterior sub-system of the DMN (Laird et al., 2009; Zuo et al., 2010). Networks 4 and 5 both comprised widespread, strongly lateralized connectivity patterns involving fronto-temporo-parietal cortex regions, which are known to be functionally integrated in a wide range of cognitive processes. Network 7 consisted of an asymmetric pattern involving, among others, the superior, middle and inferior frontal gyrus, the angular gyrus, the precuneus, and temporal regions (Biswal et al., 2010); connectivity was pronounced on the right hemisphere. Network 8 showed a connectivity cluster mainly consisting of

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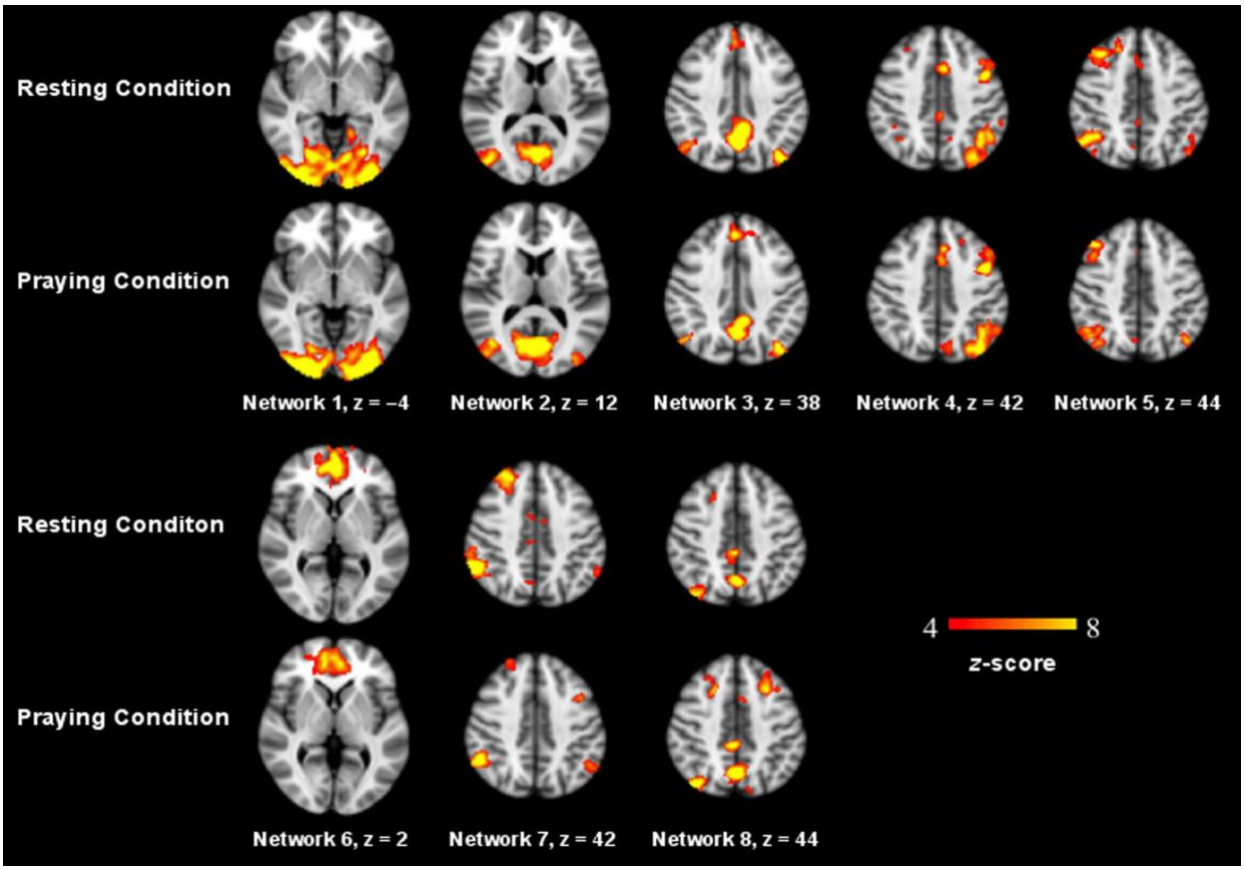

Figure 2. Functional connectivity networks detected during the conditions resting and praying the "Our Father" prayer by separate Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) approaches. Only independent components (ICs) with patterns considered networks are shown here; patterns demonstrating artificial noise were removed. Note that the order of ICs demonstrating networks was not identical between conditions; for the purpose of a better between-condition comparability, the order displayed in the praying condition is adopted to that in the resting condition. Axial images are displayed in radiological convention (z-coordinates indicated in MNI152 standard space).

the posterior cingulate cortex and the precuneus as well as the superior and middle frontal gyrus (Biswal et al., 2010).

The combined TC-GICA approach yielded 14 ICs; the same eight functional connectivity networks as in the two separate MELODIC approaches were found (Figure 3). Surprisingly, there were no significant differences in the functional connectivity of any of the detected networks between the resting and the praying conditions ($p > .05$).

Discussion

In this paradigmatic case study, we examined the functional connectivity networks of a bishop while he was praying and in a resting state condition. We found that the BOLD signals during those two states were not significantly different, leading to the conclusion that similar brain regions are involved during religious contemplation and resting. In accordance with such an interpretation, an involvement of areas associated with the default-mode brain network while praying has recently been found in highly religious people (Schjoedt, Stødkilde-Jørgensen, Geertz, & Roepstorff, 2009). Praying may therefore not only alter resting-state activation, but an assimilative process might take place, in that expertise in praying results in a state that resembles rest much more than task-related activation.

Conclusion

The case study presented here provides insight into neural processing of religious content in a same and another frame

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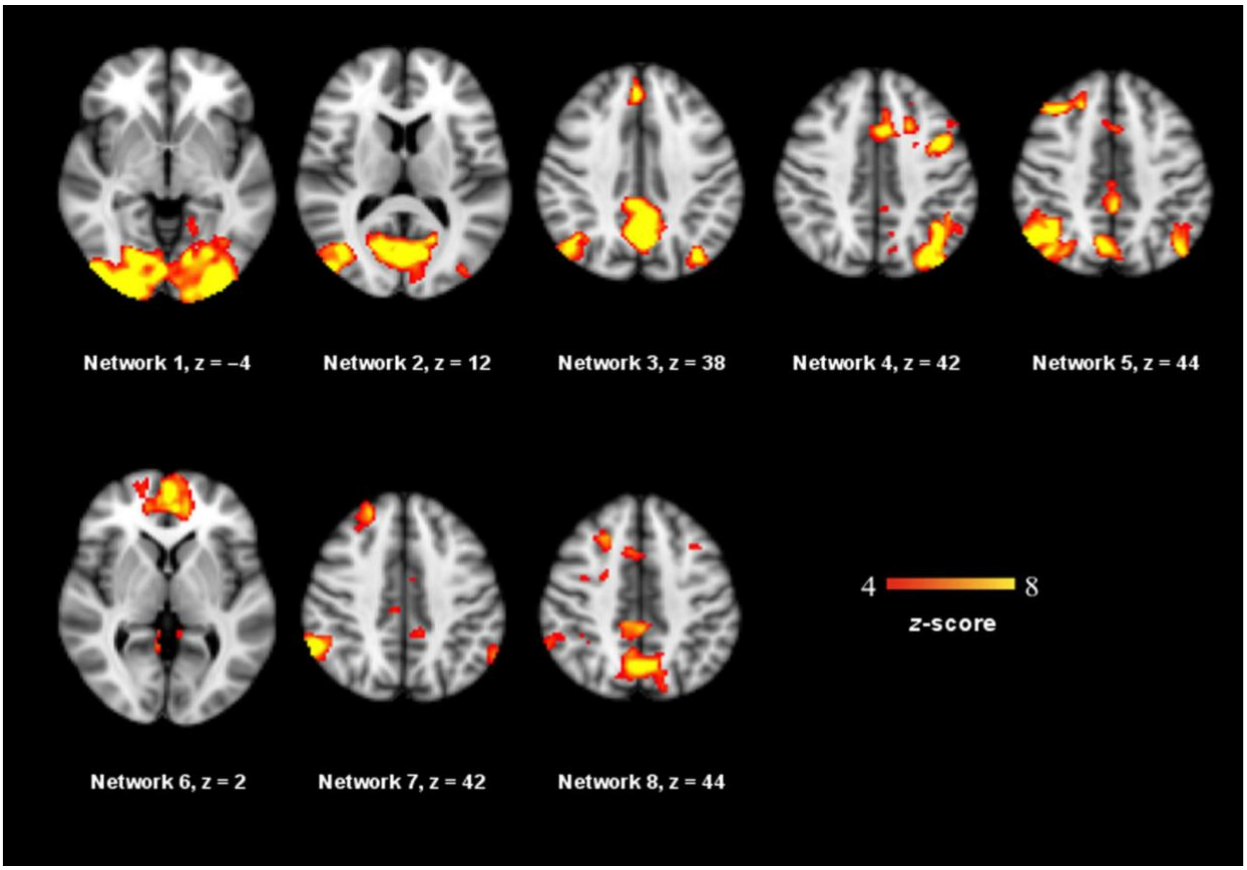

Figure 3. Neural functional connectivity networks detected in the combined evaluation using Temporal Concatenation Group Independent Component Analysis (TC-GICA). As in Figure 2, only ICs with patterns considered networks are shown here. The order of networks is adopted to that in Figure 2. Axial images are displayed in radiological convention (z-coordinates indicated in MNI152 standard space).

of reference. Expertise has consistently been found to modulate information processing, concerning perceptual, cognitive, and motor performance (Derbarnot, Sperduti, Di Rienzo, & Guillot, 2014) as well as aesthetic processes (Kirk, Skov, Christensen, & Nygaard, 2009). Being professionally bound to certain religious attitudes, norms, and beliefs might, thus, significantly shape cognitive, affective, and sensory processes. We are convinced that single case studies can be used to set up a prototype for cognitive, affective, and sensory processes (Flyvbjerg, 2006). This not only applies to clinical case studies, but also to research questions that are relevant for understanding basic aspects of human behavior and identity (e.g., Zaytseva et al., 2014).

A critical methodological remark remains: Our interpretation of the absence of effects is partly based on accepting the null hypothesis of nonsignificant effects. It remains an open question as to whether this points to an actual absence of an effect, as the absence of evidence does not imply the evidence of absence. In this sense, oftentimes the difference between significant and nonsignificant simple effects is not itself significant (Gelman & Stern, 2006). Especially concerning neuroimaging research, this highlights the need for arithmetical measures that allow for numerically more concise comparisons of brain activation states.

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5. Summary of paper IV

Self-disturbances in schizophrenia and the schizophrenia spectrum were explored in the case study of a patient with somotopsychic depersonalization in the fourth part of this thesis, published by Zaytseva et al. (2015). The patient had a depersonalization syndrome, which included a sense of being detached from one's own body and mental processes. In order to investigate the neural mechanisms underlying the behavioral alterations, a multimodal approach was used that included a clinical assessment, neuropsychological assessment, behavioral tests (alexithymia, time perception, empathy, autism spectrum quotient), and an fMRI paradigm with a task. Gibson's hypothesis of two functional systems of the sensation of touch was used to develop the fMRI task. One can infer tactile sensations by using both active and passive touch.

Several outcomes were obtained. There were no motor or sensory abnormalities diagnosed on a neuropsychological level. However, the patient did have an executive functioning deficit. On a behavioral level, we discovered a lack of empathy and higher autistic spectrum quotient scores. On a neurological level, the direct touch mode condition comparisons revealed disinhibition of the default-mode network, hypoactivation of the central executive brain networks in the performance of the touch task, and intact perceptual touch processing. These findings revealed novel characteristics of the phenomenology of somatotopic depersonalization by validating the decisions in high-order processing and intact tactile perception. They also back up the theory that the cortical midline regions play a role in the attribution of self-awareness in touch processing.

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A disembodied man: A case of somatopsychic depersonalization in schizotypal disorder

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Abstract: In the general concept of self-disturbances in schizophrenia and schizophrenia spectrum disorders, somatopsychic depersonalization (SPD) occupies a special place as it constitutes a syndrome that comprises feelings of detachment from one's own body and mental processes. However, apart from clinical descriptions, to date the pathophysiology of SPD is not fully understood due to the rareness of the syndrome and a lack of experimental studies. In a case study of one patient with schizotypal disorder, we applied a multimodal approach to understanding the SPD phenomena. The patient's clinical profile was identified as disruption of implicit bodily function, accompanied by depressive symptoms. On a neuropsychological level, the patient exhibited impairment in executive functioning, intact tactile perception and kinesthetic praxis. Behavioral tests revealed an altered sense of time but unimpaired self-agency. Furthermore, the patient exhibited a lack of empathy and he had autistic traits, although with a sufficient ability to verbalize his feelings. On the neurobiological level using an active and passive touch paradigm during functional magnetic resonance imaging (fMRI), we found a hyperconnectivity of the default-mode network and salience network and a hypoconnectivity of the central executive brain networks in the performance of the touch task as well as intact perceptual touch processing emerging from the direct comparisons of the touch conditions. Our data provide evidence for the important role of altered large-brain network functioning in SPD that corresponds to the specific behavioral and neurocognitive phenomena.

Keywords: disembodiment; fMRI; neurocognition; schizotypal disorder; self; somatopsychic depersonalization; time perception; touch
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Conceptually, depersonalization is a complex phenomenon, characterized by recurrent experiences of feeling detached from one's mental processes or body, while the reality testing remains intact (Cattell & Cattell, 1974; American Psychiatric Association, 1994). Although to date there is no evidence for the prevalence of depersonalization in schizophrenia and schizophrenia spectrum disorder, abnormal self-experiences are often met in clinical practice. One of perhaps the most troubling aspects of self-disturbances is a disembodied self (Fuchs, 2005; Fuchs & Schlimme, 2009;

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Stranghellini, 2009), with a tendency to experience an increasing distance to one's body, that is, between subjectivity and corporeality, a feeling that is termed somatopsychic depersonalization (SPD; Parnas & Handest, 2003). As Raballo (2012, p. S307) described, in SPD "[a] disturbing experiential distance emerges between the self and bodily experience, so that the body is no more a tacitly 'inhabited' aspect of selfhood but a sort of object-like, mechanic entity."

The biological underpinnings of the SPD phenomena are not yet clarified. One of the potential mechanisms of the condition is a sensory processing impairment, so-called perceptual incoherence in schizophrenia (Postmes et al., 2014). Generally, the discrimination of self and non-self and the sense of a boundary are created through proprioception and touch (Ramachandran, Hirstein, & Rogers-Ramachandran, 1998). In essence, proprioception is necessary for updating the postural body schema, whereas exteroceptive multimodal information, mainly visual, underpins the central representation and percept of the body image (Paillard, 1999). Additionally, interoception informs about the physiological condition of all tissues of the body (Craig, 2009, 2015). In patients with schizophrenia and schizophrenia spectrum disorders, the processing of the proprioceptive information may be altered as suggested by attenuated beta and gamma oscillations associated with tactile sensations (Arnfred, Mørup, Thalbitzer, Jansson, & Parnas, 2011). It has also been argued that the tacit nature and incoherent characteristics of self-disturbances are due to sensory disintegration driven by the contradictory sensory inputs or by an extreme imbalance between different sensory inputs (Ernst & Bülthoff, 2004; Postmes et al., 2014).

Neuroimaging studies are indicative of "body ownership" being governed by parietal and frontolimbic areas of the brain. Moreover, the insular cortex is discussed as the primary interoceptive cortex integrating body signals, that is, forming the experience of the bodily self (Craig, 2009, 2015). A representation of homeostatic feelings of the body would thereafter be built in the insula, which generates an experience of the bodily and emotional self at a given moment. Recent empirical work points to the decisive factor regarding schizophrenia in insular cortex dysfunction, which is additionally related to a reduced cortical connectivity between insula, dorsolateral frontal cortex, and the default mode network (DMN; Palaniyappan & Liddle, 2012; Manoliu et al., 2014).

Furthermore, key brain regions that are involved in self-processing or midline brain structures, notably the precuneus, dorsomedial prefrontal cortex, and anterior cingulate cortex, were identified (Botzung, Denkova, & Manning, 2008; Northoff & Bermpohl, 2004). These brain structures are associated with the "narrative self" including higher-order cognitive mechanisms linking them to conscious awareness (Northoff & Bermpohl, 2004). With the methodological advantages of functional brain connectivity, studies on temporal coupling of resting state functional magnetic resonance imaging (fMRI) have identified that the central executive network (CEN) is a key hub residing in the dorsolateral prefrontal cortex, which is anti-correlated with the DMN (Fox et al., 2005; van Buuren, Gladwin, Zandbelt, Kahn, & Vink, 2010). CEN exerts the "top-down" control of DMN activity and both networks constitute one dynamically balanced system. Furthermore, a specific role in the regulation of the above-mentioned networks is given to the salience network (SN) involving the dorsal-anterior cingulate and anterior insula regions, which mediate the selection of salient external and interceptive signals (Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008).

Given the complexity of the SPD, in a single-case study of a patient with schizotypal disorder, we were interested in several aspects that might contribute to the sense of disembodiment.

Firstly, capitalizing on the methodological power of fMRI, we assessed the cutaneous and kinesthetic responses from the active and passive touch paradigms. The paradigm was based on Gibson's theory of two functional subsystems of the sense of touch (1962). The cutaneous sense provides the receiver with information about the stimulation of the skin surface, whereas kinesthesis, the sensation of movement, provides dynamic information about the relative positioning of the body parts (Gibson, 1962; Loomis & Lederman, 1986). Thus, one can draw a demarcation line between the two sensory subsystems that can be termed the active and passive modes of touch. Passive touch is referred to as "tactile perception." This perception is based solely upon stimulation of the cutaneous sense. In addition to the cutaneous information, active touch also means a purposeful exploration of the stimulus field provided by afferent and efferent kinesthesis as well as the ability to control upcoming information.

Secondly, as touch may play a peculiar role in the elementary aspect of self-awareness (Husserl, 1952/1989), we addressed the recruitment of the large-scale networks that are involved in self-referential processing. Therefore, we applied a connectivity analysis of the large-scale networks,

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specifically, the DMN, CEN, and SN, in order to evaluate the patterns of their integration/disintegration of networks during the touch task.

Thirdly, self-disturbances in patients with schizophrenia spectrum disorders are associated with a number of psychological and physiological phenomena. Thus, neurocognitive impairment and notably working memory, executive functioning, and psychomotor speed deficits correspond to the intensity of anomalous self-experiences (Nelson, Whitford, Lavoie, & Sass, 2014). The study by Maggini, Raballo, and Salvatore (2002) indicated that depersonalization is deeply rooted within the difficulty of identifying or verbalizing feelings (alexithymia). Along with the verbal difficulties, self-disturbances might be connected to the lack of empathy as empathy obviously relies on "embodied" processes, such as the generation, representation and perception of feeling states (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004). Therefore, we also aimed to test the contribution of the other factors, such as neurocognitive functioning, alexithymia, and empathy correlates.

Fourthly, since the subjective sense of time in the seconds-to-minutes range relies on body feelings (Craig, 2015; Wittmann, 2013), we furthermore tested the patient's time perception capacity. The sense of time seems to be related to the temporal integration of signals from the interceptive system. For example, in a historic single-case study of a female patient with a (most likely) depersonalization syndrome, the patient had lost her sense of bodily feelings, she did not feel emotions, and she had lost any sense of time and duration (Revault D'Allonnes, 1905). Also in schizophrenia, subjective time on the level of experience as well as that assessed in psychophysical tasks is prominently altered (Martin et al., 2014).

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Informed consent was provided.

Case history

M. M., a 29-year-old Caucasian man, was diagnosed with schizotypal disorder (F.21 in the *ICD-10: International statistical classification of diseases and related health problems*; World Health Organization, 1992). He admitted to the outpatient department after approximately 12 years of ongoing symptoms. He had a positive history for neurotic disorders as his mother experienced a unipolar depression comorbid with depersonalization-derealization syndrome. There was no past history of substance use/abuse. The patient's psychiatric history dates back to the age of 15 when he was apathetic and distanced from the world and others and oftentimes experienced episodes of a lack of sensitivity of his own body. These symptoms began as episodic, and then periods between episodes decreased and lengths of episodes increased. Two years later, after a traumatic event (the death of his grandmother in an accident), the feeling of numbness of his body substantially increased. Despite these feelings, he was able to accomplish his school education and successfully entered the first year of university. At this time, he analyzed his feelings a lot, describing them as: "Parts of my body—at times parts of my body don't seem to be real or to belong to me, particularly my hand and arm." Having no rational explanation for the way he felt, he became religious and developed esoteric and metaphysical interests. He left the university and isolated himself in a monastery where he ruminated and experienced occasional transient quasi-psychotic episodes with unusual thoughts. He imagined that his soul and body were captured by demons. Moreover, the lack of body feeling became constant, and he described it as if he was a detached observer of himself. He was low in mood, experienced apathy and anhedonia. At the first outpatient visit, he primarily presented asthenia, anergia, cognitive impairment, and psychomotor retardation. He had been taking risperidone (3 mg/day), prescribed by a psychiatrist with minor improvement. Two years later, symptoms remained unchanged causing significant distress. The depressive mood, anxiety and depressive thoughts were progressing. From time to time he was tearful and had thoughts about death, but no actual suicide attempts. He was hospitalized and during hospitalization, he was often perplexed and found it very difficult to relate to other people and in general to the external world. The patient was prescribed a combination of trifluoperazine, carbamazepine, and amitriptyline, but after 6 months of treatment, the state remained unchanged. The therapy schema was substantially changed to Zyprexa (15 mg/day) and paroxetine (40 mg/day). After 6 months of treatment, there was a substantial improvement of mood; however, the depersonalization symptoms remained unchanged. In order to refine the remission, the patient was prescribed aripiprazole (5 mg/day), but no substantial improvement has been reached.

Psychiatric status

The patient was oriented with respect to time, location, and his personal identity. He looked older than his actual age,

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and was shabbily dressed. His psychomotor reactions were retarded. He appeared to be emotionally flattened with low mimic expression. He described his state in detail, and was clearly fixated on his feelings. His formal thinking ability was normal, although his speech was characterized by poverty and a lack of expressions. His main complaints were the numbness of his body, especially in his feet. He described his feelings as if his tactile feeling, temperature sensitivity, and tastes were compromised: "I am no longer myself, it is not my body. I feel like I have been pulled out of my body. Feeling is coming back only after physical exercise or when I am in pain. I feel emotionally empty; I do not feel fear anymore. Sometimes, I feel anxious though without any reason; I can't find any place." He described himself as being low in mood and feeling anxious and extremely tense when contacting other people. He reported anhedonia, and therefore a lack of interests and a meaning for life. His appetite was increased but he did not experience the taste of food. Sleep was sufficient. His total Hamilton Depressive Rating Scale (Hamilton, 1966) score reached 18 points, indicating a moderate depression.

Neurological status

Electroencephalography and computed tomography gave no evidence of brain abnormalities. Cerebral structures were completely normal for his age. Somatosensory and motor functions had no deviations from the norm. Thus, organic (neurological or general medical) causes were excluded from consideration.

Methods

Part 1: Behavioral measurements

Neuropsychological assessment

The patient underwent standardized neuropsychological testing based on Luria's systematic approach, which was done by a certified neuropsychologist (Y. Z.). The Luria diagnostic test consists of numerous procedures designed to isolate dysfunctions as compared to the more global assessment characteristics of other neuropsychological test batteries. It includes 31 tests covering verbal and visual working memory functions, motor functions, sensory skills (auditory, visual, tactile), verbal skills (expressive speech, receptive speech, reading, writing), arithmetic abilities, verbal and non-verbal reasoning, and problem-solving tasks (Glozman, 1999; Luria, 1973). Each test undergoes qualitative evaluation comprising specific errors and misperformances and quantitative evaluation on a 4-point scale with a scoring of 0 (*no deficits*), 1 (*weak*), 2 (*moderate*), and 3 (*severe*; Filatova, 2000). The Luria neuropsychological battery allows for assessing complex motor and sensory phenomena and providing a qualitative expression of the disturbance pattern level of the patient's performance (Glozman, 1999; Zaytseva et al., 2014). Referring to this specific case, we were interested in the evaluation of the kinesthetic praxis (postural praxis of each wrist, transfer of the positioning of the fingers from one hand to the other with eyes closed), cutaneous perception (localization of touch) and stereognosis (recognition of objects by touch). Handedness was assessed through the Edinburgh handedness inventory (Oldfield, 1971); the patient was right-handed.

Results of neuropsychological evaluation: Despite an average IQ and normal visual, acoustic and cutaneous perception, stereognosis and kinesthetics, the patient's scores on dynamic praxis, visuospatial analysis and synthesis, verbal and visual memory and reasoning tests had fallen by more than 1 *SD*. A summary of the performance scores is depicted in Figure 1.

In the domain of verbal memory (memorizing words, series of words, stories) the patient exhibited a marked impulsivity with a decreased productivity in the immediate recall but with stable dynamics of the learning curve. In the delayed recall, the patient experienced an increased inhibition of the stimuli by interference activity. In the tests of visual memory (memorizing six geometric figures), there

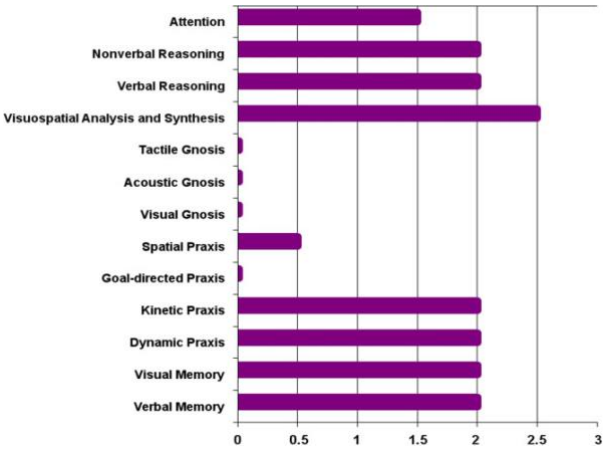

Figure 1. The quantitative results of the neuropsychological assessment. Each function underwent quantitative evaluation on a 4-point scale with a scoring of: 0 (*no deficits*), 1 (*weak*), 2 (*moderate*), or 3 (*severe*; Filatova et al., 2000).

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was a steady dynamics with a gradual increase in productivity, although the presence of macrographias, spatial errors (dysmetrias, change of proportions), and numerous sequence errors were present. The types of errors in verbal and non-verbal memory were not modality-specific, with specific contaminations between the series of stimuli that reflect executive disturbances. His performance reflected an average ability to learn and store new information. In kinetic (dynamic) praxis (fist-edge-palm test), impulsive movements, disturbances of self-monitoring and simplification of a given motor sequence program, perseverations inside the program were observed. In spatial praxis probe, there were spatial type errors, that is, mirroring of movements with the neglect of laterality and sticking to the previous elements of the probe. In visuospatial gnosis (drawing, copy of the figure) the patient presented with marked spatial function disturbances: non-withholding of the line, drawings were depicted in a planar view, and were metrically and topographically distorted, and the patient did not benefit from corrections. Attention was characterized by noticeable instability. Despite the general sufficient level of productivity, the patient was extremely slow in the execution of the tasks. Intensive cueing by the examiner was needed at all steps of the problem solutions in the verbal and non-verbal reasoning tests. Together with the general slowness, retention of the instruction and the structure of the program proved to be difficult. Thus, the most pronounced deficit was found in visuospatial functions, dynamic motor functions, and executive functioning.

Tickle test

The ability to discriminate between self-initiated touch and the touch initiated by an external source, as approached using a tickle task (Blakemore, Wolpert, & Frith, 2000), has been used as a measure of self-agency and self-monitoring. During the task, five different body parts were probed in random order: palms (left and right), feet (left and right), belly, sides of the torso (left and right), and armpits (left and right). During the task, the patient was sitting on a chair. The tickling was performed in self and experimenter conditions. Following the tickle administration, the patient was immediately asked to rate the ticklishness on a scale from 0 (*not at all*) to 10 (*extremely ticklish*).

Results of the test: The results of the test are represented in Figure 2.

M. M. consistently reported more intense tickle sensations in the experimenter condition for all body parts as compared to self-tickling, thus demonstrating a clear sense of agency.

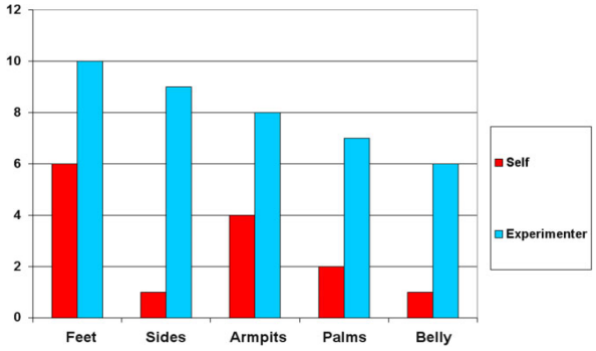

Figure 2. Tickle test results. Tickle intensity ratings are plotted as a function of a body part being tickled. Red = self-administered tickle; blue = tickling by the experimenter.

Time perception paradigms

Two computerized prospective time perception tasks were administered—a time estimation task and a time production task (Wittmann et al., 2015). For estimating time, M. M. had to judge the duration of a number-reading task that was presented for 60 s. In the time production task, the same number-reading task was administered again, but M. M. had to press a button to stop the task when 1 min had subjectively passed for him. In the simple number-reading task, which serves the purpose of preventing subjects from counting, the subject is asked to name out loud consecutive numbers that appear for 1 s on the screen with jittered pause intervals of 4, 6, or 8 s in between.

Results of the time perception and time estimation paradigms: In the time estimation task, the 60-s task was estimated as having lasted 217 s, which is more than 4 *SD* beyond the mean of a control group (overestimation). In the 60-s time production task, the patient's response was 87 s, which is more than 1 *SD* (nearly 1.5 *SD*) of the mean of a healthy control group (overproduction).

Other behavioral tests

Additionally, we applied several behavioral tests in order to evaluate the confounding personality issues. The Emotional Quotient Questionnaire (EQQ; Baron-Cohen & Wheelwright, 2004) was used to evaluate empathy (understanding of the intentions of others, experience the emotion triggered by others' emotions). The Toronto Alexithymia Scale (TAS) is a 20-item instrument and one of the most

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commonly used measures of alexithymia. The scale refers to difficulties identifying and describing emotions and the tendency to minimize emotional experience and focus attention externally (Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994). Furthermore, the Autism Spectrum Quotient (AQ) was applied to give an indication of autism spectrum disorder traits (Baron-Cohen & Wheelwright, 2004; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001).

Results of the tests: The patient's score for the EQQ was 26, indicating decreased empathic abilities. His total score on the TAS was 64, which is within the normal distribution. The results of the AQ test were a score of 25, supporting autistic tendencies slightly above the population average.

Part 2: fMRI paradigm

fMRI experimental design

Prior to the assessment, the patient was off the antipsychotic medication for 3 days. We applied a touch paradigm with a special emphasis on active task execution and passive perception. Four experimental conditions were used in the study: (a) an active touch, when the patient has to touch the human hand; (b) an active touch, when the patient has to touch a plastic hand; (c) a passive touch from a human—when the patient's hand was touched by the hand of the experimenter; and (d) a passive touch with a plastic hand—the hand of the patient was touched by the plastic hand. The experimental paradigm was based on the classical block-design: during each run, the four conditions were presented eight times each, in random order.

The task was conducted using a block-design within 32 blocks; each condition was presented eight times. Inside the MR scanner, over a head-coil compatible mirror system (300 cm screen to mirror, 15 cm mirror to subject's eyes), M. M. viewed the stimuli, the commands "TOUCH" or "WAIT" (10 s), which were followed by a 5-s pause. The "TOUCH" command indicated the active condition, when the patient had to touch a hand but was not aware whether it would be a human or a plastic hand. The "WAIT" command alerted the patient that he now would be touched, without an indication as to which hand, human or plastic, would be touching. The stimuli were presented in randomized order. The hand of the patient was lying in a pronated position. A plastic, life-size prosthesis of a female right hand was placed on the table between the participant's hands (15 cm to the left of the participants' right hand). The actions of the experimenter outside the scanner were synchronized with the experiment. The patient did not know who was the experimenter. After each trial, the patient was asked a question as to whether the touching hand was plastic or human and chose the answer by pressing a response button.

The experiment was conducted on a 1.5-Tesla Siemens Scanner, equipped with a standard head coil. The subject's head was securely but comfortably fastened by foam cushioning in order to minimize head movements. For blood oxygen level dependent functional imaging, a T2*-weighted Echo-Planar Imaging (EPI) sequence was used with the following parameters: repetition time = 2500 ms, echo time = 50 ms, flip angle = 87°, number of slices = 38, slice thickness = 4 mm, inter-slice gap = 0.4 mm, ascending acquisition, field of view = 1248 × 1248 mm, matrix = 64 × 64, and in-plane resolution = 3.25 × 3.25 mm. Functional images were acquired in axial orientation, covering the whole cerebrum and dorsal cerebellum.

Data preprocessing and analysis

Data were analyzed with Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Motion artifacts were detected with ARTREPAIR toolbox, and abnormal slices were repaired. All functional images were realigned, spatially normalized into standard stereotaxic space (EPI template; Montreal Neurologic Institute), resliced to 2 × 2 × 2 mm voxels, and smoothed with an 8-mm full-width at half maximum Gaussian kernel. Statistical parametric maps were thresholded at $p < .001$ (uncorr.). Anatomical description was done referring to the AAL atlas (Automated Anatomical Labelling of Activations; Tzourio-Mazoyer et al., 2002) from the MRIcroN (http://www.sph.sc.edu/comd/rorden/mricron).

Connectivity analysis

Data were decomposed into functional networks using a spatial independent component analysis as implemented in the GIFT toolbox (http://icatb.sourceforge.net). Subject-specific spatial maps and time courses were acquired using back reconstruction type based on PCA compression and projection, implemented in GIFT software (Calhoun & Adali, 2006). We characterized a subset of components as independent component networks (ICNs) with the peak activation in grey matter and minimal or no overlap with the vascular ventricular or edge regions that correspond to head motion. We also ensured that the mean power spectra of the selected ICN time courses showed higher low-frequency spectral power. The cluster stability quality (Iq) index of these ICNs over 20 ICASSO runs very high (Iq ≥ 0.9) for all

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Table 1
Neurofunctional Correlates of the Touch Modes in the Four Main Experimental Conditions

Conditions	Cluster	kE	Peaks				Brain area
			x	*y*	*z*	*Z*-value	
Active touch vs. baseline	1	3341	−52	−26	58	Inf.	L. superior parietal g., L. postcentral g.
	2	2208	32	−44	64	5.61	R. superior parietal g., R. postcentral g.
	3	562	44	58	−12	4.44	R. frontal mid g., R. superior frontal orbital g.
Passive touch vs. baseline	1	2601	−46	−18	56	Inf.	L. superior parietal g., L. postcentral g.
	2	1451	46	−20	54	5.76	R. superior parietal g., R. postcentral g.
Active human vs. passive human	1	3888	8	−52	12	5.45	L. precuneus, L. cuneus, L. calcarine g.
	2	1260	62	−34	18	5.11	R. superior temporal g.
	3	126	−4	22	64	4.65	Suppl. motor area
	4	320	54	−46	38	4.22	R. supramarginal g., R. inferior parietal g.
	5	502	48	32	2	4.14	R. inferior frontal tri. g.
	6	120	−64	6	8	4.14	L. rolandic oper g.
Active plastic vs. passive plastic	1	121	−12	−50	8	3.83	L calcarine g.
	2	124	−22	−66	−8	3.76	L. inferior temporal g.
Active plastic vs. active human	1	205	−30	−58	58	4.18	L. superior parietal g.
Passive plastic vs. passive human	1	102	62	−36	14	4.20	R. superior temporal g.

Note. kE = cluster size.

of the components. Eventually, four ICNs out of the 20 components were labeled as components of interest. Components time series went through additional post-processing to remove remaining noise sources. The post-processing steps included: detrending, regression of six motion parameters, despiking, and band pass filtering (0.01–0.15 HZ). Subsequently, the selected four components, which were sorted temporally using multiple regression employing the study design matrix and the time courses of the components, were plotted.

Results of the comparison between conditions

Concerning the different tasks, the patient was able to recognize the human and plastic hands with 100% accuracy. Initially, the conjunction analysis included all four experimental touch modes contracted with the baseline, which revealed a bilateral activation of the superior parietal gyri and postcentral gyri. Additionally, the right frontal superior orbital gyrus was activated in the active conditions (Table 1, Figure 3A).

Subsequently, to define brain areas particularly involved in processing active and passive touch with a human/plastic hand on the voxel-by-voxel level, we conducted several pairwise comparisons between experimental conditions.

The comparison between active human and passive human touch ($AH > PH$) revealed activation of the precuneus, left calcarine and left cuneus, which together constituted the biggest cluster of activation in the brain. We also observed activations of the superior temporal gyrus, supplementary motor area, right inferior frontal cortex, right supramarginal gyrus, and left rolandic operculum (Figure 3B). There was no difference in the reverse comparison ($PH > AH$).

For active plastic hand touch as compared to passive hand touch, activations were registered in the left calcarine gyrus, left lingual gyrus, and left temporal inferior gyrus. No difference was found in the reverse contrast ($PP > AP$) (Figure 3C).

Additionally, we also observed an increased activation of the superior parietal gyrus in active plastic hand touch as compared to the active human hand touch and an increased activation of the superior temporal gyrus as a neural response to the passive plastic hand touch in comparison to the passive human hand touch.

Results of the connectivity analysis

From 20 predefined networks, we preselected the four networks of interest, specifically large-scale networks and somatomotor networks in order to test our hypothesis. The first network encompassed the anterior part of the DMN, including the dorsolateral prefrontal cortex, which is known to be involved in decision-making, emotional processing, and monitoring of actions (Raichle et al., 2001). The second network included the anterior part of the CEN, specifically the inferior frontal gyrus, which is responsible for executive functions: impulse control, emotion and behavior control, planning, goal and value orientation, power of judgment, etc. (van Buuren et al., 2010). The third network involves the dorsal-anterior cingulate and anterior insula regions, which mediate the selection of salient external and interceptive

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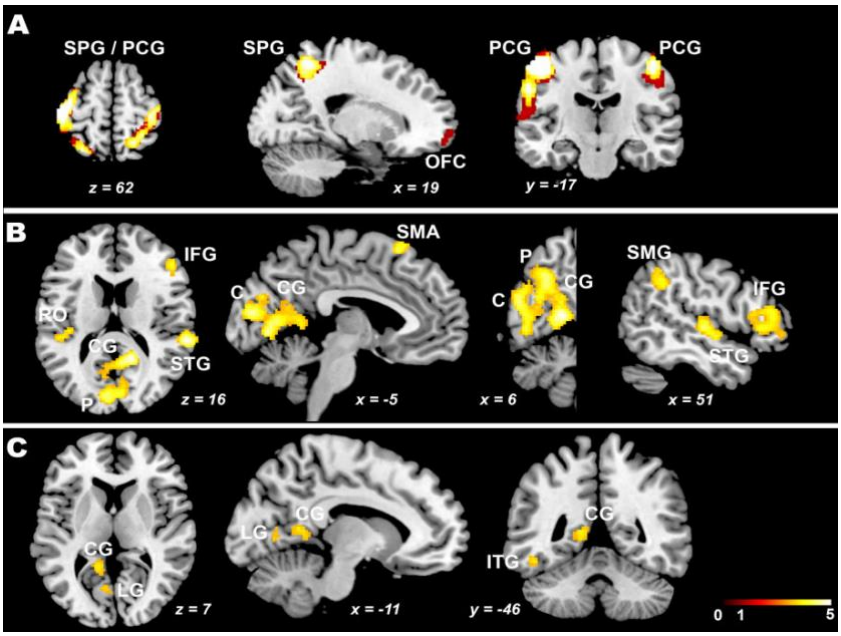

Figure 3. Neurofunctional correlates of touch modes. (A) Conjunctions of (1) active touch vs. baseline (in red) and (2) passive touch vs. baseline (in yellow). Statistical parametric maps ($p < .001$, uncorr.). *X* coordinates are Montreal Neurologic Institute (MNI) coordinates. *SPG* = superior parietal gyrus; *PCG* = postcentral gyrus; *OFC* = orbitofrontal cortex. (B) Neurofunctional correlates of active human and passive human touch. Statistical parametric maps ($p < .001$, uncorr.). *X* coordinates are MNI coordinates. *P* = precuneus; *C* = cuneus; *CG* = calcarine gyrus; *SMA* = supplementary motor area; *RO* = rolandic operculum; *STG* = superior temporal gyrus; *SMG* = supramarginal gyrus; *IFG* = inferior frontal gyrus. (C) Neurofunctional correlates of active plastic and passive plastic touch. Statistical parametric maps ($p < .001$, uncorr.). *X* coordinates are MNI coordinates. *CG* = calcarine gyrus; *LG* = lingual gyrus; *ITG* = inferior temporal gyrus.

signals (Menon & Uddin, 2010; Sridharan et al., 2008). The fourth somatomotor network comprised the paracentral lobule, superior parietal lobule, and supplementary motor area (Uncapher, Hutchinson, & Wagner, 2010). The latter supports attention, action intention, spatial perception, etc.

The analysis of the time series revealed substantial alterations of active human touch processing. While the patient exhibited an activation of the somatomotor network, the CEN was deactivated and the DMN and SN networks were activated. On the contrary, in other conditions, somatosensory networks remained stable, except for the passive human touch when it was activated. The large-scale networks showed a regular pattern: the activation of the CEN and deactivation of the DMN; the SN was relatively stable (Figures 4–6).

Discussion

With this single case study we aimed at investigating the neural mechanisms underlying the sensory and executive alterations of the experiences of a disembodied self.

First, our study did not show a specific sensory deficit in the patient with SPD. With respect to activity of brain regions, touch conditions elicited large clusters of activation in the parietal cortex that are commonly reported in fMRI studies with tactile paradigms (Ebisch et al., 2013). Interestingly, active touch revealed an additional activation of the orbitofrontal cortex associated with having control over directed movements (see also Gremel & Costa, 2013). Our findings support the hypothesis of Gibson (1962) on the tactual perceptions of the modes of touch. In this particular case, we were able to disentangle the active and passive touch processing. On the one hand, active and passive touch incorporated perceptual experiences expressed by different tactile sensations, which were mirrored by different brain activations. On the other hand, active goal-directed movement resulted in additional information provided by afferent and efferent kinaesthesis and the control of action. The orbitofrontal cortex, which possibly subserves this function, is known to be involved in goal-directed behavior and has a pivotal role within the mesocortical pathway (Takahashi et al., 2009). The fact that the activity of the somatomotor areas of the cortex is preserved is also supported by the intact neuropsychological evaluation of the tactile gnosis and kinesthetic praxis (similar to a previous study, Zaytseva, Gurovich, Sarkisyan, & Sarkisyan, 2011).

Secondly, we found a striking pattern in the brain networks processing active touch. Goal-directed activity ordinarily elicits the deactivation of the DMN and activation of the CEN. However, the patient exhibited a reverse pattern of this activity. There is ample evidence of the hyperactivity of the DMN in schizophrenia spectrum patients (Whitfield-Gabrieli & Ford, 2012). It was also suggested that deficits in attention and working memory are correlated with distinct alterations in functional coupling, particularly

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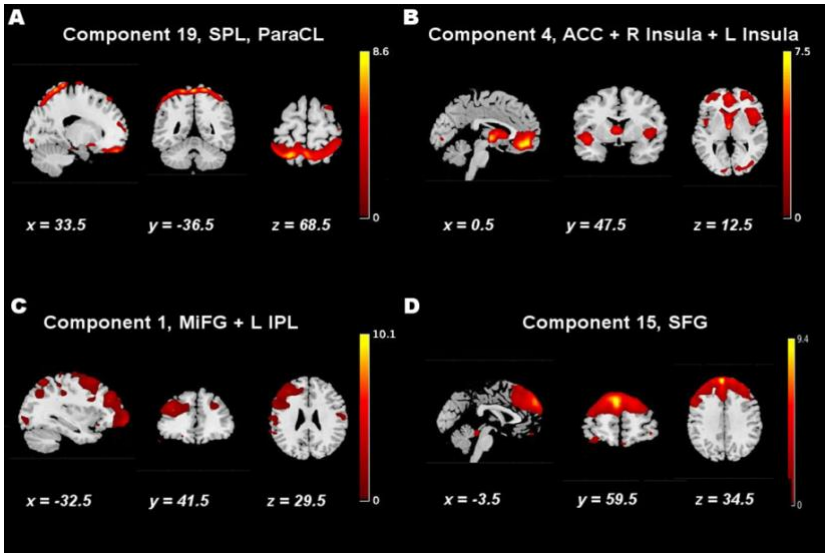

Figure 4. Composite maps of the four networks of interest with component labels and peak coordinates. (A) Component 19: Somatomotor network. *SPL* = superior parietal lobule; *ParaCL* = paracentral lobule. (B) Component 4: Salience network. *ACC* = anterior cingulate; *R Insula* = right insula; *L Insula* = left insula. (C) Component 1: Central executive network. *MiFG* = middle frontal gyrus; *L IPL* = left inferior parietal lobule. (D) Component 15: Default mode network. *SFG* = superior frontal gyrus.

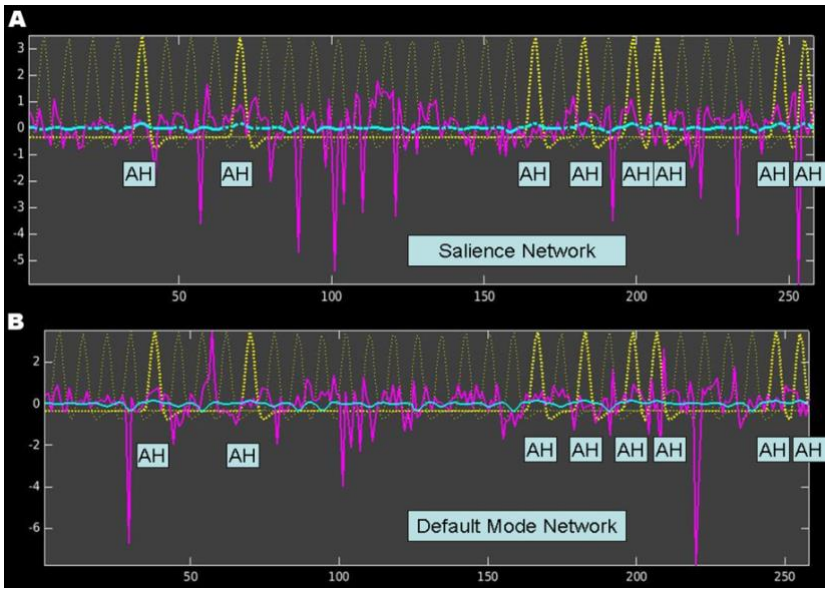

Figure 5. ICA time courses of (A) salience network; and (B) default mode network. Yellow line = block-paradigm; Pink = ICA time course; Blue = linefit to ICA represents least squares approximation of the ICA. AH = active human touch.

hyperactivity of the DMN, suggesting schizophrenia-related dysregulation of inhibitory brain circuits (Repovš & Barch, 2012; Whitfield-Gabrieli et al., 2009). These findings are in line with the findings of executive functioning deficits (poor reasoning) in our patient. The deficit in these cognitive functions is well reported in schizophrenia spectrum patients (for a review see Barch & Ceaser, 2012) and is confirmed by various structural and functional neuroimaging studies. Specifically, in one voxel-based morphometry study, cognitive deficits were directly related to brain volume abnormalities in frontal and temporo-parietal cortices in first-episode patients, most specifically in inferior portions of the dorsolateral prefrontal cortex (Minatogawa-Chang et al., 2009).

Thirdly, although we did not apply specific tools to assess self-agency, the patient demonstrated activation of the precuneus in the active touch mode. As part of the cortical midline structures, precuneus activity has been discussed to be associated with self-referential processing (Cavanna &

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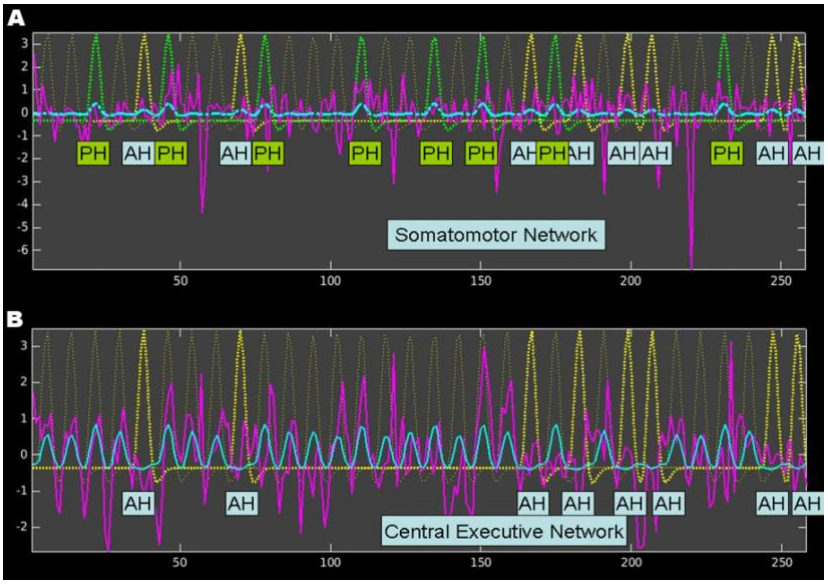

Figure 6. ICA time courses of (A) somatomotor network; and (B) Central Executive Network. Yellow line = block-paradigm; Pink = ICA time course; Blue = linefit to ICA represents least squares approximation of the ICA. AH = active human touch; PH = passive human touch.

Trimble, 2006). Our patient also showed a clear sense of agency as assessed by the implicit measure (tickle test). Self-processes can be categorized into high- and low-order processes, for example, as proposed by Nelson, Thompson, and Yung (2012): pre-reflective level (minimal self, basic bodily self, self-agency) and reflective self (narrative self, autobiographically extended self; Cermolacce, Naudin, & Parnas, 2007; Mishara, 2007). It has been recently proposed that the minimal self is possibly connected to multisensory integration processes (Nelson et al., 2012), potentially related to the processing of the bodily self through insular cortex activation (Wittmann, 2015), whereas the narrative self is associated with the higher level of synthetic brain activity involving midline brain structures (Northoff et al., 2006; Zaytseva et al., 2014). Therefore, further studies of depersonalization might benefit from the differentiated approach in addressing these self-related processes.

Our study also did not confirm the findings of Maggini and colleagues considering alexithymia as a component of depersonalization (Maggini et al., 2002). At the same time, we found low empathic and high autistic traits in the patient that might have contributed to the phenomenon of depersonalization.

Finally, regarding the sense of time, M. M. showed a distorted sense of duration in the duration estimation task and only a slightly deviating performance from normative data in the duration production task. That is, in the behavioral task of pressing a button after 1 min, M. M. was above 1 *SD* of the healthy norm group. In the task of estimating the duration of 1 min, M. M. showed a pronounced overestimation beyond 4 *SD* from the norm group. This latter finding is an indication that subjective time in M. M. is distorted. Typically, in studies testing a group of healthy subjects, estimates of duration correlate negatively with productions of duration (e.g. Siegman, 1962). In testing M. M. as an individual, we can only speculatively conclude that the task constraints differentially affected timing performance. In the case of duration production, the task demand to concentrate for a pre-specified and verbalized duration might have helped in producing a time interval that only moderately deviated from the norm. The time estimation task, in contrast, seems to disclose that M. M. is strongly "lost in time" in the time range around 1 min. Since it has been proposed that the sense of time in the seconds-to-minutes range relies on bodily feelings (Craig, 2015; Wittmann, 2013), this noticeable deviation in time perception could be a further indication that M. M. suffers from subjective changes in his body sense.

Conclusions

In this paper we have attempted to draw parallels between clinical, neuropsychological, neuroscientific, and behavioral investigations of a patient with somatopsychic depersonalization. We identified the following profile: a disruption of the implicit bodily function, depressive symptoms, intact tactile perception and kinaesthetic praxis, impairment in

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executive functioning, unimpaired self-agency, lack of empathy and autistic traits, sufficient ability to verbalize one's own feelings, and noticeable deviations in the estimation of time. On the neurobiological level, we found a disinhibition of the DMN and hypoactivation of the CEN in performance of the touch task as well as intact perceptual touch processing as it emerged from the direct touch mode condition comparisons. From the above discussion concerning the symptoms that the patient is presenting, it is most likely due to the disintegration of the connectivity of large-scale networks and frontal lobe dysfunction rather than any specific and localized neural dysfunction. The role of the large-scale networks was highlighted in a recent study suggesting that consciousness results from widespread communication amongst brain networks rather than from localized, specific brain areas (Heine et al., 2012). With increasing conscious awareness, the functional connectivity within these networks increases (Godwin, Barry, & Marois, 2015).

Bodily feeling is essential for creating a sense of the self. In the particular case of M. M., an increasing subjective distance to the body and to himself (disembodiment) is illustrated by the dissociation between the patient's subjective experiences of the symptoms (numbness of the limbs, subjective reports of tactile insensitivity, etc.) and the objective measures, which did not show deviations. In other words, M. M. may cognitive-emotionally misinterpret the signals coming from his body that seem to be intact. Presumably, such altered perceptions arise rather from impairments in higher-order cognitive and interpretive functioning related to a disturbed self than from a sensory deficit.

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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6. Summary of paper V

In the fifth part of this thesis, published by Han et al. (2014), we looked at emotional expressions about autobiographical experiences rather than semantic information. The role of vocal expression of emotions (EE) was studied in retrieving events from autobiographical memory in 21 Alzheimer's disease (AD) patients and 19 healthy controls. The participants took part in an autobiographical interview designed to assess four categories of memory retrieval: current (yesterday, last week, last month), and distant recollections. Eight independent Raters examined the memory reports (tracks with recorded voices) (three Europeans familiar with the Korean language and five Koreans).

The Raters scored the emotional intensity of the subject's voice on a 0–2 rating scale after listening to each track, and the evaluation was blind in terms of a group membership. The EE in distant memories was well retained in both groups, whereas the EE in recent memories was significantly altered. Because cognitive degradation indicated by cognitive testing preceded the loss in expression of emotion, the amount of emotional expression corresponded to cognitive functioning. The benefit of the applied design was that it made an indirect allusion to questions of personal identity, which are closely linked to autobiographical memory.

Self-continuity and personal identity depend on episodic events maintained in autobiographical memory. Our findings suggest that alterations in emotional expressiveness may have an impact on self-processing.

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Impairment of vocal expression of negative emotions in patients with Alzheimer's disease

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Vocal expression of emotions (EE) in retrieval of events from autobiographical memory was investigated in patients in early stages of Alzheimer's disease (AD). Twenty-one AD patients and 19 controls were interviewed, and EE of the reported memories was rated by 8 independent evaluators. The AD group had lower EE of both recent and remote memory than controls, although EE in remote memories was better preserved in both groups. We observed positive correlations between EE and indicators of cognitive competence in AD patients. AD Patients are impaired in the ability to express emotions already at early stages of the disease, and EE seems to deteriorate along with the progression of cognitive impairment.

Keywords: Alzheimer's disease, emotional expression, vocal expression, autobiographical memory, episodic memory

INTRODUCTION

Expression and recognition of emotions are essential for social communication. It is well established that emotions enhance episodic and autobiographical memory (Tulving, 1987); this functional relationship between memory and emotions is supported by observations indicating that memories for events can be intensified by strong emotional valence (Bower, 1992), and the recall is commonly better for emotionally colored autobiographical events (Holmes, 1970; Brewer, 1988; Wang, 2008; Rasmussen and Berntsen, 2009). Autobiographical memory is not only the encoding and retrieval of sets of information, but also remembering one's own past event in its integrative detail grasping particular objects, emotions or feelings, thoughts, and senses related to that event.

Memory impairment is a hallmark of Alzheimer's disease (AD). The difficulty in encoding and/or retrieval of new information is claimed to be one of the earliest symptoms in patients with AD (Murphy et al., 2008; Leyhe et al., 2009; Irish et al., 2011a; Bastin et al., 2012). It is known that remote memories in AD are better preserved than the recent ones (Sartori et al., 2004; Leyhe et al., 2009). At the same time, emotion processing in AD patients appears to be altered which to a certain degree influence negatively the quality of patient's interaction with others (Bucks and Radford, 2004). The recent study of Irish et al. (2011a) reported the disruption of emotional re-experiencing in retrieval of recent autobiographical memories in AD patients.

Emotions are recognized and expressed in several ways: nonverbally using facial expression and gestures and verbally or vocally; in the latter case the prosody of language, its intonation pattern, its rhythmic structure, and speech velocity are commonly used to index emotional processes (Berry, 1975; Bachorowski and Owren, 1995; Mozziconacci, 2002; Owren et al., 2005; Pöppel, 2010). During communication in humans, information about speaker's emotional state is conveyed by the modulation of tone of the voice, namely emotional prosody. Explicit judgments about emotional states using emotional prosody evaluation are commonly used as a method for psychological therapy effectiveness in a variety of neurological and psychiatric diseases (van den Broek, 2004; Quadfliega et al., 2007).

Previous research on autobiographical memory and emotions, including studies on AD has been mainly focused on the recognition of emotions but rarely on emotional expression. Specifically, Burton and Kaszniak (2006) observed the emotional expression in AD patients recording facial muscle activities. They found small changes in the zygomatic activity in AD patients. Henry et al. (2009) reported mixed results on the lack of amplification of emotions and intact suppression of emotions in response to the emotional stimuli (watching comedy film segments) in AD patients indicating disrupted regulation of expressed emotions. However,

to date there are no studies on the vocal emotional expression of autobiographical memory retrieval in AD even though it could be a critical cue of diagnosis and therapy.

In the present study, we investigated vocal expression of emotions (EE) in the retrieval of autobiographical memory in the early stage of AD. We hypothesize that the emotional expression of AD patients is expected to be lower than in healthy individuals of the same age. Since remote memory is better preserved in Alzheimer's patients we expect that the expression of that memories will be more intense due to close relatedness to salient life events. As a general assumption, one could also predict that alterations in emotional expression develop in parallel with cognitive deterioration as emotional processing and cognition are densely linked (Pessoa, 2008). For verifying these hypotheses, we used an explicit evaluation of vocal expression of emotion in the retrieval of subject's own autobiographical memory. Such method proved to be ecologically valid (Scherer, 2003). It allows rather to measure quality of memory's retrieval than its quantity. Indeed, the analysis of subjects' own past memory is difficult to interpret in terms of accuracy of responses as compared to other validated quantitative methods, however, we attempted to improve the validity of the method controlling for homogeneity of memory recalls, concentrating only on the negative memories retrieval. We followed the argument of Berntsen (2002) claiming that the emotionally negative memories like traumatic events contain more important information to the survival than positive memories.

MATERIALS AND METHODS

SUBJECTS

Twenty-one patient with AD (10M/11F, age = 61.84 ± 5.2 years; years of education = 9.19 ± 4.92) and 19 matched healthy elderly controls (9M/10F, age = 61.84 ± 3.74 years; mean education = 11.26 ± 3.89) participated in the study. All patients were selected on the basis of neurological examination, neuropsychological testing from Korean-Dementia Rating Scale (K-DRS) (Choi, 1998), Mini Mental State Examination-Korean (MMSE-K) (Kwon and Park, 1989) and CT/MRI scan. Patients were diagnosed with early stage of dementia (K-DRS > 106; MMSE-K range = 20–27) within 69 years at the most in accordance to the criteria of National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). Healthy elderly controls were volunteers recruited from the local community, and were all in good mental and physical health. We applied the following exclusion criteria: a history of alcoholism, epilepsy, psychiatric illnesses including depression, significant head injury for both groups. The study was approved by the ethic committee of the KyungHee University Medical Centre (KHNMC-OH-IRB 2009-015), and all subjects provided informed consent for study participation.

PROCEDURE

The subjects underwent autobiographical interview, which was purposely designed for measuring four categories of retrieval of recent (yesterday, last week, last month) and remote memories. No cues were used, thus subjects recalled memories freely. In the remote memory retrieval, subjects were asked to report the most impressive event from their childhood. Most subjects recalled the evacuation during the Korean War. As all subjects experienced the war in their childhood, those who did not spontaneously recall the event of Korean War were asked for it. For the recent memories, at first subjects were asked to retrieve any impressive event of the last month, last week, and yesterday. An MP3 player recorded verbal responses during the test.

As a first step, four different episodes of a subject's retrieved memories from each category were selected by experimenters (four persons including the interviewer with Ph.D. degree in human biology), who did not participate in the further experiment. The contextually negative emotional events were chosen as the majority of subjects did not recall any positive emotional events during free recall procedure. The most vocally emotionally expressed parts were selected for the next step of the experiment. Each selected track contained the record of voice (neutral passages reporting participant's everyday life) for 10 s followed by the pause (5 s) and 30 s of retrieval of negative experiences.

As a second step, eight evaluators (age = 27.75 ± 4.09, 4M/4F, three Europeans familiar with Korean language and five Koreans) were recruited to perform emotional expression (EE) rating.

Before the procedure, all evaluators were given a detailed instruction and underwent a training of emotional expression evaluation. The training was conducted by two educated instructors (graduated school students: one Korean and one European). The recorded tracks were played randomly (recent and remote memories mixed). After listening to each track evaluators subsequently rated the emotional intensity of subject's voice on 0–2 rating scale: 0 – unrelated to emotion, 1 – related, 2 – highly related. While rating, evaluators were asked to subjectively create a mental synthesis of the prosody and tone of the voice, its intonation, the rhythmic structure and velocity of speech including crying and laughing sounds which in all cases proved to be possible. For all conditions, the evaluators were blind with respect to group membership.

STATISTICAL ANALYSIS

The data were analyzed using Statistical Package for the Social Science (SPSS version 12.0). Results were expressed as means and SD for demographic data and cognitive functions, and Median for memories scores. We used χ^2-tests complemented with the effect sizes in order to analyze differences in the proportion of patients and controls in categories of emotional expression (yesterday, last week, last month, remote) and Wilcoxon test for within-group comparison of recent (composite scores for yesterday, last week, and last month) versus remote memories. The sum scores were calculated for each memory category (rating scores of all eight evaluators were summed up) as well cognitive scores in order to indicate emotional expression and cognitive functioning competences. Correlative analysis between vocal expression (recent and remote) and cognition test scores, which were derived from K-DRS (i.e., attention, initiation–perseveration, construction, conceptualization, and memory) was done using Spearman correlation coefficient. Inter-rater reliability was calculated using Fleiss Kappa coefficient for multiple raters.

Table 1 | Subjects' and evaluators' demographic data.

	Age in years (mean and SD)	Sex	Education in years (mean and SD)	MMSE-K scores (mean and SD)	K-DRS scores (mean and SD)
Controls ($n = 19$)	61.84 ± 3.74	Male: 9 Female: 10	11.26 ± 3.89	27.89 ± 1.28*	$135.52 + 4.09$*
AD ($n = 21$)	61.84 ± 5.2	Male: 10 Female: 11	9.19 ± 4.92	23.19 ± 3.62	121.28 ± 9.74
Evaluators ($n = 8$)	27.75 ± 4.09	Male: 4 Female: 4	19.13 ± 1.89	–	–

*$p < 0.01$.

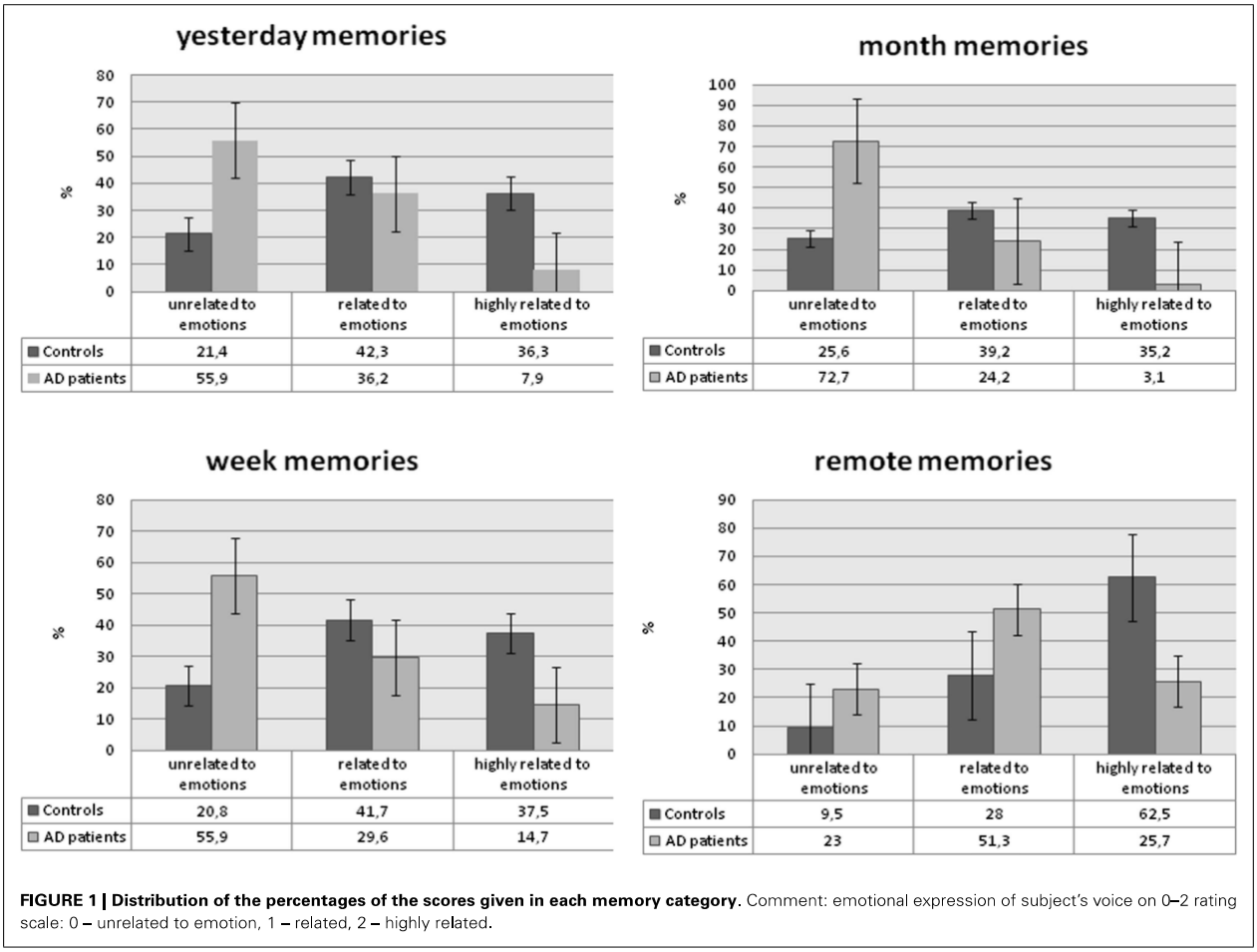

FIGURE 1 | Distribution of the percentages of the scores given in each memory category. Comment: emotional expression of subject's voice on 0–2 rating scale: 0 – unrelated to emotion, 1 – related, 2 – highly related.

RESULTS

Demographical and clinical data on patients, controls as well as evaluators group are presented in **Table 1**.

A significantly higher proportion of AD patients' memories was rated as 0–1 (not-related to emotions/related to emotions) whereas EE of controls were more likely to be rated as 1–2 (related to emotions/highly related to emotions) in all four categories of memories ($\chi^2 = 34.09$, $p < 0.0001$ with effect size $r = 0.65$ for yesterday memories; $\chi^2 = 28.13$, $p < 0.0001$, effect size $r = 0.43$ for week memories; $\chi^2 = 53.06$, $p < 0.0001$, $r = 0.54$ for month memories; $\chi^2 = 27.82$, $p < 0.0001$, $r = 0.62$ for remote memories) (**Figure 1**).

Taking into account the similar distribution of the scores in yesterday, last week, and last month memories, the scores of these categories were merged into recent memory score, which was used for further within-group analysis. In recent versus remote memories comparison, there was a higher emotional involvement in remote memory retrieval than in recent both in AD patients ($Z = -3.36$, $p < 0.001$) and in controls ($Z = -2.48$, $p < 0.0039$).

Explorative correlation analysis between the emotional vocal expression and five cognitive functions (attention, initiation-perseveration, construction, conceptualization, and memory) in overall participants sample revealed positive correlations between EE of all memory categories (**Table 2**).

The reliability of agreement results are as follows: for yesterday memories (FK = 0.1922, SE = 0.02, 95% CI = 0.1501–0.2344), for week memories (FK = 0.5069 SE = 0.0225, 95% CI = 0.4628–0.5510), for month memories (FK = 0.2635 SE = 0.0224, 95% CI = 0.2196–0.3074), for remote memories (FK = 0.3571 SE = 0.0213, 95% CI = 0.3154–0.3988).

DISCUSSION

The present study yielded several new results. Firstly, we showed that patients with early stages of AD are impaired in the ability to express their emotions during autobiographical memory retrieval both of recent and remote memories. Previous research was focused primarily on non-verbal emotional expression in AD patients (Smith, 1995; Seidl et al., 2012), and it was performed in already severely cognitively impaired patients with AD. For the first time, we report that low vocal emotional expression is already present at an early stage of AD. In contrast to other studies, we explored emotional expressions referring to autobiographical memories rather than to semantic knowledge. Episodic experiences stored in autobiographical memory are essential to construct and to maintain a sense of personal identity and self-continuity (Piolino et al., 2009; Pöppel, 2010). Based on our findings one can conclude that changes in emotional expression might also affect self processing.

Even though the AD group showed a lower emotional expression for recent and remote events compared to the control group, the emotional expression when recalling remote memories were better preserved. These findings confirm previous results which indicated that at early stages AD patients exhibit difficulties in retrieving memories from the time after the AD's onset, but are capable of retrieving memory from long time ago (Kaszniak et al., 1993; Clare et al., 2000). This might match other observations of

Table 2 | A comparison between AD groups and healthy controls, and correlations between emotional expression and cognitive functions.

Group	Values	Yesterday (controls = 19, AD = 21)	Week (controls = 19, AD = 17)	Month (controls = 18, AD = 8)	Remote (controls = 19, AD = 20)
Controls	Mean + SD	9.73 (±3.42)	10.05 (+3.53)	10.00 (+4.36)	13.15 (+2.65)
	Median	1	1	1	2
	25–75%	1–1.5	1–2	1–2	1.5–2
AD	Mean + SD	4.14 (±2.55)	5.52 (+4.75)	5.37 (+2.38)	8.15 (+3.54)
	Median	0	0	0.75	1
	25–75%	0–1	0–1	0.5–1	1–1

K-DRS	Group	Mean (±SD)	Recent memory		Remote memory	
			Spearman *r*	*p*	Spearman *r*	*p*
CORRELATIONS BETWEEN EE AND COGNITIVE FUNCTIONS						
Attention	Controls	35.68 (±0.88)*	0.491**	0.001	0.412**	0.009
	AD	33.95 (±2.63)				
Initiation/perseveration	Controls	33.73 (±3.39)	0.452**	0.003	0.295	0.068
	AD	31.42 (±5.08)				
Construction	Controls	5.89 (±0.315)*	0.330*	0.037	0.379*	0.017
	AD	5.05 (±1.49)				
Conceptualization	Controls	36.73 (±1.72)**	0.412**	0.008	0.437**	0.005
	AD	33.85 (±3.96)				
Memory	Controls	23.47 (±1.54)**	0.700**	0.000	0.635**	0.000
	AD	16.95 (±3.52)				
Total	Controls	135.52 (±4.91)**	0.672**	0.000	0.459**	0.003
	AD	121.28 (±9.74)				
MMSE-K	Controls	27.89 (±1.28)**				
	AD	23.19 (±3.62)				

*Comment: correlative analysis was done in overall groups, *p < 0.05, **p < 0.01.*

an interaction between age and life span (Botwinick and Storandt, 1980; Perlmutter et al., 1980). Botwinick and Storandt (1980) suggested that the individuals recall those events better that happened with them when they were young adults (aged 15–25) compared to the events from the other life time period. In the current study, all subject recalled the events related to Korean War as remote memory, which they experienced as the teenagers.

Furthermore, we found that the level of emotional expression competence corresponds to the cognitive functioning. As cognitive deterioration determines dementia diagnosis, and the incremental decrease of cognitive functions is followed by the declining of the emotional expression, therefore EE might be considered as a substantial parameter in the diagnostic process.

Bucks and Radford (2004) reported that AD patients have deficit of emotional processing and cognitive functioning compared to healthy elderly adults. However, other studies (Koff et al., 1999; Lavenu et al., 1999; Han and Pöppel, 2009) have argued that a deficit in emotional processing is secondary to cognitive impairments associated with AD. For example, Koff et al. (1999) indicated that AD patients do not have a primary deficit in the processing of emotions. However, all the previous studies on emotional processing in AD used the emotional recognition tasks and identification of basic emotions. The facial expressions decrease gradually with the progression of dementia (Norberg et al., 1986) and inappropriate facial expression is present at the early stage of AD (Kunz et al., 2007). In our study, the vocal emotional expression was evaluated and appeared to be impaired in early stage of AD. It may suggest that the quality of the retrieval of autographical memory is generally declined in early stage of AD.

Furthermore, recently López-de-Ipiña et al. (2013) reported gradual changes in the spontaneous speech and emotional response in AD patients similar to the results of Kertesz and Clydesdale (1994) who observed the decline in expressive language skill in AD. As we have demonstrated, although the patients were able to recall emotional events from their own memory, they did not reproduce the events with a proper vocal expression. This finding go in line with the recent research of Irish et al. (2011b) suggesting that AD patients reproduce their own past events in fragmented and depersonalized way even though they recall evocative events.

As a limitation of the study, we report a small sample size and certain subjectivity of the external evaluation; one can predict the slight difference in scoring. However, the comparison did not reveal the substantial difference between the scores. Emotional expression in patients was more likely to be rated 0–1, while controls were mostly rated as 1–2.

In conclusion, frequent observations of caregivers suggest that AD patients in their early stages do not express sufficiently their emotions, demonstrating symptoms similar to depression and also altered communication or activity. Indeed, there are cases when such patients are misdiagnosed as being depressed. We showed here that emotional expression is affected in early stages of AD, and in patients who are not clinically diagnosed as depressed. Although, there has been an increasing interest in training of emotional expression, mainly non-verbal, our findings suggest that vocal emotional expression might be a target for therapeutic interventions.

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