UNIVERSITA' DEGLI STUDI DI PARMA

_____

DOTTORATO DI RICERCA IN NEUROSCIENZE

CICLO XXV

Emotional Motor Resonance and its Role in

Anomalous Subjective Experience in Schizophrenia

Coordinatore:
Chiar.mo Prof. Vittorio Gallese

Tutor:
Chiar.mo Prof. Vittorio Gallese

Tesi di dottorato della dott.ssa Mariateresa Sestito

_____

ANNO ACCADEMICO 2012-2013

INDEX

Chapter 3: MIRRORING THE SELF: TESTING NEUROPHYSIOLOGICAL CORRELATES OF DISTURBED SELF-EXPERIENCE IN SCHIZOPHRENIA SPECTRUM

Chapter 4: ANOMALOUS ECHO: EXPLORING ABNORMAL EXPERIENCE CORRELATES OF EMOTIONAL MOTOR RESONANCE IN SCHIZOPHRENIA SPECTRUM

Chapter 5: GENERAL DISCUSSION AND CONCLUSIONS   **106**

Chapter 1

1. General Introduction

When I am looking into a mirror, I do not know any more whether I am here looking at me there in the mirror, or whether I am there in the mirror looking at me here. (...) If I look at someone else in the mirror, I am not able to distinguish him from myself any more. When I am feeling worse, the distinction between me and a real other person gets lost, too. While watching TV, I don't know any more, whether I am speaking in the TV-set or whether I am hearing the words here. I don't know whether the inside turns outwards, or the outside inwards . . . Are there perhaps two 'I's?

Kimura (1994)

1.1 "When we are smiling, the whole world smiles with us": Emotional motor resonance and its relation with empathy through Mirror Neurons mechanisms.

Until recently, psychologists and cognitive scientists have spent little effort on the development of complete models of the mental processing of emotional information. Such information prioritizes attention (Ohman et al., 2001), access to word meaning (Nygaard & Lunders, 2002), and the organization of material in memory (Niedenthal & Halberstadt, 1999).

Classic models of information processing in the cognitive sciences allow sensory, motor, and emotional experience to be represented without their perceptual and experiential basis. In such models, largely inspired by the metaphor of "mind as computer", information taken from the different sense modalities is preserved in memory in the form of abstract entities. These are thought to be stored in a manner that is functionally separated from the original neural systems that encoded them in the first place, for example, those involved in vision, olfaction, and audition (Barsalou, 1999; Fodor, 1975; Newell, 1980). Such information processing models make what individuals know about emotion equivalent to what they know about most other things.

Another way to think about information processing is clustered under the label "theories of embodied cognition". Although this approach provides an original perspective and is based on methodological and technological innovation, the basic idea is actually very old (Prinz, 2002). The assertion common to such theories is that high-level cognitive processes, such as thought and language, use partial reactivations of states in sensory, motor, and affective systems during their processes. In this view, the grounding for knowledge - what it refers to - is the original neural state that occurred when the information was initially acquired. If this is true, then using knowledge is a lot like reliving past experience in at least some, and sometimes all, of its sensory, motor, and affective modalities: the brain captures modality-specific states during perception, action, and interoception and then reinstantiates parts of the same states to represent knowledge when needed. Theories of embodied cognition have now been applied to provide rigorous accounts of emotion and the processing of information about emotion (Niedenthal et al., 2005; Damasio, 1994).

One hypothesis regarding the application of theories of embodied cognition to emotion is that the perception of emotional meaning (i.e., recognizing a facial expression of emotion) involves the embodiment of the implied emotion (Gallese, 2001, 2003; Adolphs, 2002). There is now substantial empirical support for this hypothesis. Neuroimaging studies have revealed that recognizing a facial expression of emotion in another person and experiencing that emotion oneself involve overlapping neural circuits. In an illustrative study, researchers had participants inhale odors that generated feelings of disgust (Wicker et al., 2003). The same participants then watched videos of other individuals expressing disgust. Results showed that areas of the anterior insula and, to some extent, the anterior cingulate cortex were activated both when individuals observed disgust in others and when they experienced disgust themselves (related findings are reported in Lawrence et al., 2002; Carr et al., 2003). Similarly, behavioral studies demonstrate that emotional expressions and gestures are visibly imitated by observers and that this imitation is accompanied by self-reports of the associated emotional state (Chartrand & Bargh, 1999). Theories of embodied cognition provide a

6

theoretical account of why this happens: the imitation of other individuals' emotional expressions is part of the bodily reenactment of the experience of the other's state.

Normally, the induction of an emotion episode causes a coordinated suite of cognitive and physiological changes, including, at least in the case of the so-called basic emotions, a characteristic facial expression (Ekman, 1992). Interestingly, this causal relationship appears to be bi-directional. There is substantial evidence that manipulation of the facial musculature, either voluntarily or involuntarily, has a causal effect in generating, at least in attenuated form, the corresponding emotional state and its cognitive and physiological correlates. Thus, the relationship between emotion states and their facial expressions exhibits a kind of rough one-to-one correspondence in both directions.

Emotion simulation process begins with a visual representation of other's facial expression, which serves to activate facial musculature imitating this expression. That such imitation capacities exist is well established. Meltzoff and Moore (1983) found that infants as young as one-hour-old imitate tongue protrusion and a range of other facial displays, which they see modeled before them. In addition to the finding that humans can imitate the facial expressions of others, there is further evidence that humans spontaneously and rapidly activate facial musculature corresponding to visually presented facial expressions. In a series of studies, Dimberg and colleagues, found that presentation of pictures of facial expressions produces rapid, covert activation of one's own facial musculature, which mimics the presented faces (Dimberg & Thunberg, 1998; Lundquist & Dimberg, 1995). Such muscular activation occurs extremely rapidly and is often subtle, but is detectable in a valid and reliable way by means facial Electromyography (EMG) recording. The finding that subjects spontaneously, rapidly, and covertly imitate visually presented facial expressions is consistent with a model in which these self-generated facial expressions are the consequence of an antecedently generated emotion state. Support for the claim that the muscle movements are primary and in fact give rise to a subsequent emotion state comes from two lines of evidence. The first line of evidence suggesting that facial movements might occur prior to the

7

emotion experience is that there are reasons to believe that these facial movements are an instance of a more general "mirroring" phenomenon. An action mirroring system, in which internal action representations activated in the production of an action are also activated when the same action-type is observed in others, is known to exist in monkey and human ventral premotor cortex, and neighboring regions (Gallese et al., 1996; Iacoboni et al., 2001; Rizzolatti et al., 1996). Furthermore, the operation of the action mirroring system is known to generate covert activation of distal musculature. In an early experiment that helped establish an action mirroring system in humans, Fadiga and colleagues used transcranial magnetic stimulation (TMS) to enhance distal electromyographic responses (Fadiga et al., 1995). They found that observation of actions (e.g. grasping an object, tracing a figure in the air) modeled by a target, reliably produced EMG activations in the corresponding muscle groups of the observer.

Recent evidence indicates that the action mirroring system may also operate during the observation of facial expressions. An fMRI study by Carr et al. (2003) found that participants passively observing faces expressing emotions, display neural activation in the premotor cortex and neighboring regions which are normally activated in the production of facial movements, and which are in the region thought to house the action mirroring mechanism. If there is indeed an action mirroring mechanism that operates during the observation of facial expressions, it may help explain the covert activation of facial musculature discussed earlier. In other words, the phenomenon found by Dimberg and colleagues - covert activation of musculature that imitates the muscular activation patterns presented by a target - may be an instance of a mirroring phenomenon that occurs for somatic musculature more generally. As a consequence, if the facial movements found by Dimberg and colleagues are indeed an example of a more general mirroring phenomenon, they need not be explained as the result of an antecedent emotion experience.

Since involuntary facial mimicry constitutes an important low-level mechanism reflecting embodied simulation of the perceived emotion, when emotional imitation goes smoothly, there is a strong foundation for empathy (Decety and Jackson, 2004), arising as a perceived-emotion

reverberation occurring at a bodily level (Gallese, 2001; 2003; 2005; 2006; Niedenthal, 2007; Niedenthal et al., 2009). In everyday life, for example, mimicking the facial expressions of our partner is good for our relationship, even if this means that we will grow to resemble each other because we repeatedly use the same facial muscles. And surely, when we are smiling, the whole world will smile with us.

1.2 Empathy deficits in Schizophrenia: the possible role of embodied simulation disruption.

Social and emotion dysfunctions are common features of schizophrenia (Bigelow et al., 2006; Burns, 2006; Shamay-Tsoory et al., 2007; Paradiso et al., 2003; Crespo Facorro et al., 2001) that often appear before the onset of full-blown psychotic symptoms (Edwards et al., 2001; Brüne, 2005; Bertrand et al., 2008) and affect functional outcome (Couture et al., 2006). Studies of social cognition in schizophrenia have focused primarily on Theory of Mind (ToM), emotion processing, agency judgment, and empathy (Brunet-Gouet & Decety, 2006; Andreasen et al., 2008; Park et al., 2009). While ToM refers to cognitive aspects of mentalizing or the ability to draw accurate conclusions about others' cognitions and emotions (Frith & Frith, 2003; Keysers & Gazzola, 2006), empathy has both cognitive and affective components and generally refers to the capacity to recognize and share the feelings experienced by others.

Empathy is a multidimensional construct and requires the ability to perceive, understand and feel the emotional states of others. Due to the complexity of the construct (see Preston & de Waal, 2002; Singer & Lamm, 2009) various definitions exist. However, according to most models, empathy consists of at least three core components (Decety & Jackson, 2004): 1) The ability to recognize emotions in oneself and others via facial expressions, speech or behavior, 2) a cognitive component, also referred to as perspective taking or theory of mind, describing the competency to take over the perspective of another person, though maintaining the essential distinction between self and other, and 3) an affective component, i.e. sharing of emotional states with others or the

ability to experience similar emotions as others. For each of the three factors, several studies reported significant impairments of schizophrenia patients.

One proposed theory for the ability to understand mental states of others is the simulation theory, which is generally hypothesized to be a mechanism for experiencing others' sensory, motor, perceptual, and emotional experiences as if they were one's own (Preston & de Waal, 2002). One proposed mechanism for this simulation approach is through the mirror neuron mechanism, instantiated by a set of specialized neurons that become active both during motor action and during the observation of another individual's motor action (Rizzolatti & Craighero, 2004; Keysers & Gazzola, 2006). Since its original discovery, studies of mirror neurons activity have been extended to the sensory domains and most recently there have been studies examining the role of the mirror neuron mechanism in the emotional field. For example, two studies have shown that self-reported empathy is associated with activity in brain areas showing the mirror neuron mechanism (Zaki et al., 2009; Hooker et al., 2010). Patients with schizophrenia tend to show dysfunctional empathizing abilities (Brüne, 2005; Montag et al., 2007; Shamay-Tsoory et al., 2007; Benedetti et al., 2009; Derntl et al., 2009; Herold et al., 2009). These may be related to structural and functional deficits of the mirror neuron mechanism and imitation network (Bertrand et al., 2008; Fujiwara et al., 2008; Mier et al., 2010; Park et al., 2011). The mirror neuron mechanism may support appreciation of the self/other boundaries and understanding others' intentions, and its breakdown may originate psychotic symptoms (Frith & Corcoran, 1996; Gallese 2003; Brüne, 2005; Langdon et al., 2010). For example, people with schizophrenia tend to make false interpretations of other people's intentions, which may result in misperception of benign social cues as threats (paranoid delusions) or hallucinations (Arbib & Mundhenk, 2005; Bentall et al., 2009). Previous studies of mirror neuron function in schizophrenia using various neuroimaging methods have suggested that people with schizophrenia have reduced mirror neuron activity (Enticott et al., 2008) that may relate to lower ability to distinguish between actions of self and others (Schurmann et al., 2007) or empathizing deficits (Varcin et al., 2010). It has also been suggested that the degree of altered empathy and

10

social cognition in schizophrenia may be related to the state of the illness including active psychosis (Andreasen et al., 1986; Frith & Corcoran, 1996; Fahim et al., 2004; Salvatore et al., 2007). The combination of higher than normal self-agency and low self-awareness is then thought to lead to the development of delusions and psychosis (Frith, 2005).

1.3 Is the mirror broken in Schizophrenia? Investigating facial reactions in response to dynamic emotional stimuli in different modalities in healthy individuals and schizophrenia patients.

Emotional facial expression communicates feelings, but is also an important low-level mechanism contributing to the experience of empathy, thereby lying at the core of social interaction. Schizophrenia is associated with pervasive social cognitive difficulties that include emotional processing of facial expressions. Despite such disorder might play a crucial role in empathizing deficits and consequently impoverished social skills, previous research on facial expression of emotions in schizophrenia has not yielded unequivocal results. In particular, it remains unaddressed the issue of patients´ facial expression as a medium of empathic resonance contributing to the recognition and evaluation of the perceived emotion expressed by others.

In the first study described in chapter 2, we aimed at investigating whether subjective facial mimicry affects the quantitative evaluation of the emotional content of perceived emotions presented through dynamic expressive stimuli, in healthy participants and in patients diagnosed with schizophrenia. To this purpose, we employed a novel paradigm by means of which emotional dynamic ecological stimuli were presented in the visual and auditory modalities in isolation and congruently or incongruently associated. This approach enabled us to study the dimensional quality and possible alteration of the emotional responses in these two experimental groups.

1.4 "What is it like to be a person with Schizophrenia in the social world?" Looking for anomalous subjective experience correlates of emotional motor resonance in schizophrenia spectrum patients.

In recent years, the issues of subjective experiences occurring in Schizophrenia have become central topics in psychopathological research. Among self-experiential disturbances, basic symptoms, stemming from Jasperian phenomenological psychopathology, are considered the first subjective reverberation of the entailed neurobiological underpinnings of schizophrenia. Anomalous subjective experiences have been demonstrated to occur in different schizophrenia-related conditions (i.e., full-blown schizophrenia, prodromal conditions, schizotipy, and among genetically high-risk individuals) (Møller & Husby, 2000; Klosterkötter et al., 2001; Parnas et al., 1998; Parnas et al., 2005; Schultze-Lutter et al., 2007a; Schultze-Lutter et al., 2007b; Schultze-Lutter et al., 2007c; Parnas et al., 2003; Chapman & Chapman, 1987; Parnas, 2000; Handest & Parnas, 2005) thus fostering research on the underlying psychobiological processes by means of a prominent emphasis on schizophrenia experiential and behavioral manifestations. Over recent years, some researchers have argued that insights from phenomenological psychiatry may be usefully applied to early intervention efforts, in the areas of early identification (Nelson et al., 2008; Parnas, 2005), prediction of outcome (Nelson et al., 2008), and therapeutic work (Nelson et al., 2009).

Basic symptoms are subtle phenomena privately experienced by the patients, clinically devoid of accompanying observable signs, belong to the subjective experience domain. Basic symptoms have been conceived (Huber, 1983) as the first phenomenological correlate of disturbances that underlie psychopathological manifestations of the disorder. Thus, basic symptoms are likely to identify subtle expressions of genetic liability to schizophrenia, subjectively perceived as unelaborated, yet discomforting, interferences in daily experience (Huber, 1983; 1992; Gross, 1989). Phenomenology oriented researchers have proposed that principally, a disturbance of the basic sense of the self is a phenotypic trait marker of psychotic vulnerability of Schizophrenia Spectrum (SzSp) disorders (Nelson et al., 2008; Parnas, 2000; 2003; Parnas et al., 2005; Parnas et

al., 1998; Sass & Parnas, 2003). Disturbances of basic self-experience evident in SzSp conditions include disturbed sense of presence, corporeality, stream of consciousness, self-demarcation and existential reorientation, all of which are intimately interrelated (Parnas, 2003; Parnas & Sass, 2001).

Up to now however, little is known about the physiological and neurobiological underpinnings of disturbed self experiences. This is particularly important given the marked gap between patients' complaints (that generally entail disturbing experiences) and what are the most prominent schizophrenia etio-pathogenetic theories and therapeutic practices (which are by large postulated at a brain level of description and analysis). Indeed, until now, nobody has ever found a direct association between phenomenological experience (i.e., the *mind level*) and physiology (i.e., the *body level*) in schizophrenia disorder.

In the study described in chapter 3, we investigated if there is a direct connection between subjective experience (i.e., the *mind* level) as indexed by the BSABS scale, and the physiological mechanisms (i.e., the *body* level), explored through the motor facial mimicry in response to emotional stimuli, that has been successfully proved to be a mirror motor resonance *proxy* (Arbib & Mundhenk, 2005; Carr et al., 2003; Gazzola et al., 2006; Molnar-Szakacs et al., 2006; Seitz et al., 2008). In order to do this, we employed the same multimodal paradigm used in the study described in chapter 2, that proved to be sensitive in evoking a congruent facial mimicry (measured by means physiological facial Electromyographic activity, EMG) through multimodal stimuli. This paradigm has proven to detect deficits in facial mimicry in schizophrenia patients (Sestito et al., 2013).

Besides, in the study described in chapter 4, we explored whether a weak or high emotional motor resonance occurring in SzSp patients (considered as a mirror motor resonance *proxy* and thus, again, the *body* level) is related to patients' clinical features and to their anomalous subjective experiences (i.e., the *mind* level) as indexed by the BSABS scale. In order to do this, we employed the same multimodal paradigm used in previous studies presented in chapters 2 and 3.

To explore what subjective anomalous experiences characterize SzSp patients with a different degree of motor resonance to emotional stimuli, participants were divided into two groups, based on their low (i.e., Internalizers) and high (i.e., Externalizers) emotional resonance, following the same method used in previous work (Sestito et al., 2013). Clinical features (positive and negative symptoms, length of illness, age at first psychosis and number of psychotic episodes) and anomalous subjective experiences (BSABS scores) differences between these two cohorts have been then explored.

References

Adolphs, R. (2002). Recognizing emotion from facial expressions: Psychological and neurological mechanisms. *Behav Cognit Neurosci Rev.* 1, 21-62.

Andreasen, N.C., Nasrallah, H.A., Dunn, V., Olson, S.C., Grove, W.M., Ehrhardt, J.C., Coffman, J.A., and Crossett, J.H. (1986). Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. *Archives of General Psychiatry.* 43, 136–144.

Andreasen, N.C., Calarge, C.A., and O'Leary, D.S. (2008). Theory of mind and schizophrenia: a positron emission tomography study of medication-free patients. *Schizophr Bull.* 34, 708–719.

Arbib, M.A., and Mundhenk, T.N. (2005). Schizophrenia and the mirror system: an essay. *Neuropsychologia.* 43, 268–280.

Barsalou, L. W. (1999). Perceptual symbol systems. *Behav Brain Sci.* 22, 577-660.

Benedetti, F., Bernasconi, A., Bosia, M., Cavallaro, R., Dallaspezia, S., Falini, A., Poletti, S., Radaelli, D., Riccaboni, R., Scotti, G., and Smeraldi, E. (2009). Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. *Sch Res.* 114, 154–160.

Bentall, R.P., Rowse, G., Shryane, N., Kinderman, P., Howard, R., Blackwood, N., Moore, R., and Corcoran, R. (2009). The cognitive and affective structure of paranoid delusions: a transdiagnostic investigation of patients with schizophrenia spectrum disorders and depression. *Archives of General Psychiatry.* 66, 236–247.

Bertrand, M.C., Achim, A.M., Harvey, P.O., Sutton, H., Malla, A.K., and Lepage, M. (2008). Structural neural correlates of impairments in social cognition in first episode psychosis. *Social Neuroscience.* 3, 79–88.

Bigelow, N.O., Paradiso, S., Adolphs, R., Moser, D.J., Arndt, S., Heberlein, A., Nopoulos, P., and Andreasen, N.C. (2006). Perception of socially relevant stimuli in schizophrenia. *Sch Res.* 83, 257–267.

Brüne, M. (2005). "Theory of mind" in schizophrenia: a review of the literature. *Sch Bull.* 31, 21–42.

Brunet-Gouet, E., and Decety, J. (2006). Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. *Psychiatry Research.* 148, 75–92.

Burns, J. (2006). The social brain hypothesis of schizophrenia. *World Psychiatry.* 5, 77–81.

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., and Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A.* 100, 5497–5502 .

Chapman, L.J., and Chapman, J.P. (1987). The search for symptoms predictive of schizophrenia. *Schizophr Bull.* 13:497–503.

Chartrand, T.L., and Bargh, J.A. (1999). The chameleon effect: the perception-behavior link and social interaction. *Pers Soc Psychol.* 76, 893-910.

Couture, S.M., Penn, D.L., and Roberts, D.L. (2006). The functional significance of social cognition in schizophrenia: a review. *Sch Bull.* 32, S44–S63.

Crespo Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., and Hichwa, R.D. (2001). Neural substrates of emotional processing in schizophrenia. A PET study during exposure to pleasant and unpleasant odors. *JAMA.* 286, 427–435.

Damasio, A.R. (1994). *Descartes' Error: Emotion, Reason, and the Human Brain.* New York: Grosset/Putnam.

Decety, J., and Jackson, P.L. (2004). The functional architecture of human empathy. *Behav. Cognit. Neurosci. Rev.* 3, 71-100.

Derntl, B., Finkelmeyer, A., Toygar, T. K., Hülsmann, A., Schneider, F., Falkenberg D. I., and Habel, U. (2009). Generalized deficit in all core components of empathy in schizophrenia. *Schizophr Res.* 108, 197-206.

Dimberg, U., and Thumberg, M. (1998). Rapid facial reactions to emotional facial expressions. *Scand J Psychol.* 39, 39-45.

Edwards, J., Pattison, P.E., Jackson, H.J., and Wales, R.J. (2001). Facial affect and affective prosody recognition in first-episode schizophrenia. *Sch Res.* 48, 235–253.

Ekman, P. (1992). Are there basic emotions? *Psychological Review.* 99, 550–553.

Enticott, P.G., Hoy, K.E., Herring, S.E., Johnston, P.J., Daskalakis, Z.J., and Fitzgerald, P.B. (2008). Reduced motor facilitation during action observation in schizophrenia: a mirror neuron deficit? *Sch Res.* 102, 116–121.

Fadiga, L., Fogassi, L., Pavesi, G., and Rizzolatti, G. (1995). Motor facilitation during action observation: A magnetic stimulation study. *Journal of Neurophysiology.* 73, 2608–2611.

Fahim, C., Stip, E., Mancini-Marie, A., Boualem, M., Malaspina, D., and Beauregard, M. (2004). Negative socio-emotional resonance in schizophrenia: a functional magnetic resonance imaging hypothesis. *Medical Hypotheses.* 63, 467–475.

Fodor, J. (1975). *The Language of Thought.* Cambridge: Harvard University Press.

Frith, C.D. (2005). The neural basis of hallucinations and delusions. *Comptes Rendus Biologies.* 328, 169–175.

Frith, C.D., and Corcoran, R. (1996). Exploring 'theory of mind' in people with schizophrenia. *Psychological Medicine.* 26, 521–530.

Frith, U., and Frith, C.D. (2003). Development and neurophysiology of mentalizing. *Philos Trans R Soc Lond B Biol Sci.* 358, 459–473.

Fujiwara, H., Shimizu, M., Hirao, K., Miyata, J., Namiki, C., Sawamoto, N., Fukuyama, H., Hayashi, T., and Murai, T. (2008). Female specific anterior cingulate abnormality and its association with empathic disability in schizophrenia. *Progress in Neuro Psychopharmacology & Biological Psychiatry.* 32, 1728–1734.

Gallese, V. (2001). The 'shared manifold' hypothesis: From mirror neurons to empathy. *J Consc Stud.* 8, 33-50.

Gallese, V. (2003). The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology.* 36, 171-180.

Gallese, V. (2005). Embodied simulation: From neurons to phenomenal experience. *Phenomenol Cogn Sci.* 4, 23-48.

Gallese, V. (2006). Intentional attunement: A neurophysiological perspective on social cognition and its disruption in autism. *Brain Res.* 1079, 15-24.

Gallese, V., Fadiga, L., Fogassi, L., and Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, 119, 593–609.

Gazzola, V., Aziz-Zadeh, L., and Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. *Curr Biol.* 16, 1824-1829.

Gross, G. (1989). The 'basic' symptoms of schizophrenia. *Br J Psychiatry*.155, S21–S25.

Handest, P., and Parnas, J. (2005). Clinical characteristics of first-admitted patients with ICD-10 schizotypal disorder. *Br J Psychiatry.* 48, s49–s54.

Herold, R., Feldmann, A., Simon, M., Tenyi, T., Kover, F., Nagy, F., Varga, E., and Fekete, S. (2009). Regional gray matter reduction and theory of mind deficit in the earlyphase of schizophrenia: a voxel-based morphometric study. *Acta Psychiatrica Scandinavica.* 119, 199–208.

Hooker, C.I., Verosky, S.C., Germine, L.T., Knight, R.T., and D'Esposito, M. (2010). Neural activity during social signal perception correlates with self-reported empathy. *Brain Res.* 1308, 100–113.

Huber, G. (1983). Das Konzept substratnaher Basissymptome und seine Bedeutung für Theorie und Therapie schizophrener Erkrankungen. *Nervenarzt.* 54, 23-32.

Huber, G. (1992). Konzeption der Einheitspsychose aus der Sicht der Basisstörungslehre. In C. Mundt, H. Sass (Eds), *Für und wider die Einheitspsychose.* (pp. 61–72). New York, Thieme Stuttgart.

Iacoboni, M., Koski, L. M., Brass, M., Bekkering, H., Woods, R. P., Dubeau, M., Mazziotta, J. C., and Rizzolatti, G. (2001). Reafferent copies of imitated actions in the right superior temporal cortex. *Proceedings of the National Academy of Science USA.* 98, 13995–13999.

Keysers, C., and Gazzola, V. (2006). Towards a unifying neural theory of social cognition. *Progress in Brain Research.* 156, 379–401.

Kimura, B. (1994). Psychopathologie der Zufaelligkeit oder Verlust des Aufenthaltsortes beim Schizophrenen. *Daseinsanalyse.* 11, 192–204.

Klosterkotter, J., Hellmich, M., Steinmeyer, E.M., and Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry.* 58, 158–164.

Langdon, R., Ward, P.B., and Coltheart, M. (2010). Reasoning anomalies associated with delusions in schizophrenia. *Sch Bull.* 36, 321–330.

Lawrence, A. D., Calder, A. J., McGowan, S. W., and Grasby, P. M. (2002). Selective disruption of the recognition of facial expressions of anger. *Neuroreport.* 13, 881-884.

Lundqvist, L. O., and Dimberg, U. (1995). Facial expressions are contagious. *J Psychophysiol.* 9, 203-211.

Meltzoff, A.N., and Moore, M.K. (1983). Newborn infants imitate adult facial gestures. *Child development.* 54, 702-709.

Mier, D., Sauer, C., Lis, S., Esslinger, C., Wilhelm, J., Gallhofer, B., and Kirsch, P. (2010). Neuronal correlates of affective theory of mind in schizophrenia out-patients: evidence for a baseline deficit. *Psychological Medicine.* 40, 1607–1617.

Møller, P., and Husby, R. (2000). The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. *Schizophr Bull.* 26, 217–232.

Molnar-Szakacs, I., Kaplan, J., Greenfield, P.M., and Iacoboni, M. (2006). Observing complex action sequences: the role of the fronto-parietal mirror neuron system. *Neuroimage.* 33, 923-935.

Montag, C., Heinz, A., Kunz, D., and Gallinat, J. (2007). Self-reported empathic abilities in schizophrenia. *Sch Res.* 92, 85–89.

Newell, A. (1980). Physical symbol systems. *Cognit Sci.* 4, 135-183.

Nelson, B., Sass, L.A., and Skodlar, B. (2009). The phenomenological model of psychotic vulnerability and its possible implications for psychological interventions in the ultra-high risk ('prodromal') population. *Psychopathology.* 42, 283-292.

Nelson, B., Yung, A. R., Bechdolf, A., and McGorry, P. D. (2008). The phenomenological critique and self-disturbance: Implications for ultra-high risk ("prodrome") research. *Schizophr Bull.* 34, 381-392.

Niedenthal, P. M. (2007). Embodying emotion. *Science* 316, 1002-1005.

Niedenthal, P. M., Barsalou, L. W., Winkielman, P., Krauth-Gruber, S., and Ric, F. (2005). Embodiment in attitudes, social perception, and emotion. *Personality and social psychology review*. 9, 184-211.

Niedenthal, P. M., Halberstadt, J. B., and Innes-Ker, A.H. (1999). Emotional response categorization. *Psychol Rev.* 106, 337.

Niedenthal, P. M., Winkielman, P., Mondillon, L., and Vermeulen, N. (2009). Embodiment of emotion concepts. *J Pers Soc Psychol.* 96, 1120-1136.

Nygaard, L. C., and Lunders, E. R. (2002). Resolution of lexical ambiguity by emotional tone of voice. *Mem Cogn.* 30, 583-593.

Öhman, A., Flykt, A., and Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. *J Exp Psychol Gen.*130, 466.

Paradiso, S., Andreasen, N.C., Crespo Facorro, B., O'Leary, D.S., and Hichwa, R.D. (2003). Emotion in unmedicated patients with schizophrenia evaluated with Positron Emission Tomography. *Am J Psychiatry.* 160, 1775–1783.

Park, K.M., Kim, J.J., Ku, J., Kim, S.Y., Lee, H.R., Kim, S.I., and Yoon, K.J. (2009). Neural basis of attributional style in schizophrenia. *Neuroscience Letters.* 459, 35–40.

Park, I.H., Ku, J., Lee, H., Kim, S.Y., Kim, S.I., Yoon, K.J., and Kim, J.J. (2011). Disrupted theory of mind network processing in response to idea of reference evocation in schizophrenia. *Acta Psychiatrica Scandinavica.* 123, 43–54.

Parnas, J. (2000). The self and intentionality in the pre-psychotic stages of schizophrenia: A phenomenological study. In D. Zahavi (Ed.), *Exploring the self: Philosophical and psychopathological perspectives on self-experience* (pp. 115-148). Amsterdam, Netherland: John Benjamins.

Parnas, J. (2003). Self and schizophrenia: A phenomenological perspective. In T. Kircher & A. David (Eds.), *The self in neuroscience and psychiatry* (pp. 127-141). Cambridge, UK: Cambridge University Press.

Parnas, J. (2005). Clinical detection of schizophrenia-prone individuals: Critical appraisal. *British Journal of Psychiatry-Supplementum.* 48, s111-112.

Parnas, J., Handest, P., Jansson, L., and Saebye, D. (2005). Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology.* 38, 259–267.

Parnas, J., Handest, P., Sæbye, D., and Jansson, L. (2003). Anomalies of subjective experience in schizophrenia and psychotic bipolar illness. *Acta Psychiatr Scand.* 108, 126–133.

Parnas, J., Jansson, L., Sass, L.A., and Handest, P. (1998). Self-experience in the prodromal phases of schizophrenia. *Neurol Psychiatry Brain Res.* 6, 97–106.

Parnas, J., and Sass, L.A. (2001). Self, solipsism, and schizophrenic delusions. *Philosophy, Psychiatry, & Psychology*. 8, 101-120.

Preston, S. D., and De Waal, F. B. M. (2002). Empathy: Its ultimate and proximate bases. *Behav Brain Sci.* 25, 1-20.

Prinz, J.J. (2002). *Furnishing the Mind: Concepts and Their Perceptual Basis.* Cambridge: Massachusetts Institute of Technology Press.

Rizzolatti, G., and Craighero, L. (2004). The mirror-neuron system. *Annual Review of Neuroscience.* 27, 169–192.

Rizzolatti, G., Fadiga, L., Gallese, V., and Foggasi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research.* 3, 131–141.

Salvatore, G., Dimaggio, G., and Lysaker, P.H. (2007). An intersubjective perspective on negative symptoms of schizophrenia: implications of simulation theory. *Cognitive Neuropsychiatry.* 12, 144–164.

Sass, L.A., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr Bull.* 29, 427-444.

Schultze-Lutter, F., Klosterkoetter, J., Picker, H., Steinmeyer, E.M., and Ruhrmann, S. (2007a). Predicting first-episode psychosis by basic symptom criteria. *Clin Neuropsychiatry.* 4, 11–22.

Schultze-Lutter, F., Ruhrmann, S., Hoyer, C., Klosterkoetter, J., and Leweke, F.M. (2007b). The initial prodrome of schizophrenia: different duration, different underlying deficits? *Compr Psychiatry.* 48, 479–488.

Schultze-Lutter, F., Ruhrmann, S., Picker, H., von Reventlow, H.G., Brockhaus-Dumke, A., and Klosterkoetter, J. (2007c). Basic symptoms in early psychotic and depressive disorders. *Br J Psychiatry.* 51, s31–s37.

Schurmann, M., Jarvelainen, J., Avikainen, S., Cannon, T.D., Lonnqvist, J., Huttunen, M., and Hari, R. (2007). Manifest disease and motor cortex reactivity in twins discordant for schizophrenia. *The British Journal of Psychiatry.* 191, 178–179.

Seitz, R.J., Schäfer, R., Scherfeld, D., Friederichs, S., Popp, K., Wittsack, H.J., Azari, N.P., and Franz, M. (2008). Valuating other people's emotional face expression: a combined functional magnetic resonance imaging and electroencephalography study. *Neuroscience.* 152, 713-722.

Sestito, M., Umiltà, M.A., De Paola, G., Fortunati, R., Raballo, A., Leuci, E., Maffei, S., Tonna, M., Amore, M., Maggini, C. and Gallese, V. (2013). Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front Human Neurosci.* doi: 10.3389/fnhum.2013.00368.

Shamay-Tsoory, S.G., Shur, S., Harari, H., and Levkovitz, Y. (2007). Neurocognitive basis of impaired empathy in schizophrenia. *Neuropsychology.* 21, 431–438.

Singer T. and Lamm C. (2009). The social neuroscience of empathy. *Ann N Y Acad Sci.* 1156, 81-96.

Varcin, K. J., Bailey, P. E., and Henry, J. D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. *J Int Neuropsychol Soc.* 16, 621-629.

Zaki, J., Weber, J., Bolger, N., and Ochsner, K. (2009). The neural bases of empathic accuracy. *Proceedings of the National Academy of Sciences of the United States of America*. 106, 11382–11387.

Wicker, B., Keysers, C., Plailly, J., Royet, J. P., Gallese, V., and Rizzolatti, G. (2003). Both of Us Disgusted in< i> My</i> Insula: The Common Neural Basis of Seeing and Feeling Disgust. *Neuron*. 40, 655-664.

Chapter 2

2. Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study

2.1 Introduction

Emotional expressions are widely acknowledged as essential in communicating internal feelings and intentions (Ekman and Oster, 1979). The ability to communicate and understand the emotional states of others and their intentions is a fundamental social skill. Indeed, facial expressions are among the most common and significant emotion stimuli.

To this end, it is well known that humans react to emotional facial expressions with specific, congruent facial muscle mimicry, which can be reliably measured by electromyography (EMG; e.g. Dimberg, 1982; 1988). For example, pictures of sad facial expressions evoke increased muscle *Corrugator Supercilii* activity, while pictures of happy facial expressions increase muscle *Zygomaticus Major* activity and decrease muscle *Corrugator Supercilii* activity (Lundqvist and Dimberg, 1995; Han et al., 2012). These facial muscular reactions appear to be spontaneous and automatic (Dimberg and Thunberg, 1998; Dimberg et al., 2000; Dimberg et al., 2002; Larsen et al., 2003). Many studies demonstrated that facial mimicry contributes to recognition of specific facial expressions (for a rewiew, see Goldman and Sripada, 2005; Niedenthal et al., 2010). Indeed, blocking facial mimicry impairs recognition of facial expression of emotions (Oberman et al., 2007). Furthermore, it has been proposed that mimicry reflects internal embodied simulation of the perceived facial expression in order to facilitate understanding of its emotional meaning (Gallese, 2003; 2005; 2006; Halberstadt et al., 2009; Niedenthal, 2007; Niedenthal et al., 2009) and promoting empathy by means one's facial feedback system (for a review of the facial feedback hypothesis, see Adelmann and Zajonc, 1989). A recent EMG study (Dimberg et al., 2011) showed that high empathic people, with respect to low empathic group, are particularly sensitive in reacting with facial reactions when they look to emotional facial expressions. Moreover, high empathic

people rated perceived facial emotional expressions as more intense with respect to low empathic ones.

Historically, affective features of schizophrenia were considered an integral part of the disorder. Bleuler (1950) considered affective disturbance to be a fundamental symptom of schizophrenia, whereas hallucinations and delusions were regarded as accessory symptoms. Studies on patients' facial mimicry in response to emotional stimuli showed that they activate the same muscle of control subjects, but such activation was found to be weaker in patients than in healthy controls (Earnst et al. 1996; Kring and Earnst, 1999). Another study showed, on the other hand, that in contrast to healthy controls, patients diagnosed with schizophrenia demonstrated atypical facial mimicry, which was not associated with any clinical feature of the disorder. The authors of this study suggested that this evidence might account for a low-level disruption contributing to empathy deficits in schizophrenia (Varcin et al., 2010). Similarly, Wolf et al. (2006) found an undecipherable and bizarre mimic pattern within a sample of patients suffering from schizophrenia, called "*mimic disintegration*" (see Heimann and Spoerri, 1957). Mimic disintegration is defined as the inability to organize specific facial muscle movements as an integrated whole, thus making difficult for observers to decode the emotional state and establish contact or develop a deeper relationship with the patients. Furthermore, many studies investigating everyday life of patients diagnosed with schizophrenia documented an emotional-affective pattern characterized by many negative and few positive experiences, thus making patients' affectivity more negative. Some studies (Mattes et al., 1995; Iwase et al., 1999; Wolf et al., 2004; 2006) found a minor activity of *Zygomaticus* muscle in response to positive stimuli, whereas another study (Sison et al., 1996) found an overall major activation of *Corrugator supercilii* muscle, interpreted as a sign of the negative attitude showed by patients in everyday life.

Reduced emotional expression (i.e., flat affect) is not only a typical symptom of full-blown schizophrenia (Andreasen 1984a; Bleuler, 1950). Many findings lend support to the assumption that vulnerability to schizophrenia may be subtly manifested in emotional behavior long before the onset

of clinical symptoms. Furthermore, after schizophrenia onset, flat affect increases (Walker et al., 1993). Reduced emotional facial expression could be a disease risk index for high-vulnerability subjects (e.g., Schizotypal Personality patients and first degree relatives) (Phillips and Seidman, 2008). Moreover, previous research on flat affect showed a disjunction between the expression and the experience of emotion in schizophrenia (Bleuler, 1950; Berenbaum and Oltmanns, 1992; Kring et al., 1993; Kring and Earnst, 2003; Kring and Neale, 1996; Aghevli et al., 2003). These studies showed that patients with schizophrenia often reported experiencing strong emotions, but they were significantly less expressive than controls. Thus, observers could note no visible sign of emotion.

The studies using EMG recording to investigate emotional expression in schizophrenia, used different materials and methods. In particular, often non ecological stimuli, like static images non-facial stimuli, or fiction movies were used. Many studies indeed highlighted, on the other hand, the importance of dynamic stimuli in the evaluation of emotional expression. A recent study on healthy individuals showed that presentation of dynamic facial expressions evokes stronger EMG responses than static ones. Moreover, participants rated dynamic expressions as more intense that static ones (Rymarczyk et al., 2011).

Emotional facial expression communicates feelings, but is also an important low-level mechanism contributing to the experience of empathy, thereby lying at the core of social interaction. Schizophrenia is associated with pervasive social cognitive difficulties that include emotional processing of facial expressions. Despite such disorder might play a crucial role in empathizing deficits and consequently impoverished social skills, previous research on facial expression of emotions in schizophrenia has not yielded unequivocal results. In particular, it remains unaddressed the issue of patients´ facial expression as a medium of empathic resonance contributing to the recognition and evaluation of the perceived emotion expressed by others.

The aim of this study was to investigate whether subjective facial mimicry affects the quantitative evaluation of the emotional content of perceived emotions presented through dynamic expressive stimuli, in healthy participants and in patients diagnosed with schizophrenia. To this

purpose we employed a novel paradigm by means of which emotional dynamic ecological stimuli were presented in the visual and auditory modalities in isolation and congruently or incongruently associated. This approach enabled us to study the dimensional quality and possible alteration of the emotional responses in these two experimental groups.

2.2 Methods

Participants

Thirty participants took part to the experiment. Control participants (CNT; ten males, five females, mean age 35.8 years SE +/- 2.3) were recruited by public announcement and were blind to the experimental goals. None of them reported the presence of any neurological or psychiatric disorder. Patient group (SZP; ten males, five females, mean age 32.8 years SE +/- 1.7) were recruited from the Clinical Psychiatry Institute of the University of Parma. All of them were chronic clinically stable outpatients, mainly diagnosed with schizophrenia, paranoid subtype. Only one patient was diagnosed with a disorganized subtype, one with an undifferentiated subtype and two patients with a residual subtype. Psychiatric diagnosis was established via a structured interview (Structured Clinical Interview for DSM–IV, SCID). Exclusion criteria were the presence of neurological and vascular disorders, dysmetabolic syndrome, alcohol or drugs abuse and mental retardation (Intelligence Quotient score <70). All participants had normal or corrected to normal vision. In addition to being closely matched for gender, the two groups did not differ in age (t_{30}= -1.06, $p>0.05$). All clinical participants (SZP) were receiving antipsychotic medication (most of them were administered new generation atypical antipsychotics). Since the age of onset and the illness duration indicated that the clinical sample was heterogeneous, for comparing dosages of different drugs we converted doses of medication to chlorpromazine equivalents. Then we multiplied these equivalents by the time an individual had been on a given dose to obtain cumulative value measured in dose-years. After each dose had been converted to dose-years, the

results could be summed to provide a cumulative measure of lifetime exposure (Andreasen et al., 2010).

In order to describe psychopathological features related with schizophrenia, patients were administered a variety of tests: Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b), Social Anhedonia Scale (SAS; Chapman et al., 1976), Physical Anhedonia Scale (PAS; Chapman et al., 1976). Given that all patients were under medication, we also administered them the Simpson-Angus Extrapyramidal side-effects Scale (Simpson and Angus, 1970), an established, valid and reliable instrument for assessing neuroleptic-induced parkinsonism (Janno et al., 2005). None of them were beyond cut-off value, indicating that SZP participants did not show any significant extrapyramidal side-effect related with drugs assumption. Details about CNT and SZP samples are provided in Table 1. Written informed consent was obtained from all participants before entering the study. The local Ethical Committee approved the study.

Table 1. Demographic variables and characteristics of Schizophrenia (SZP) and Control (CNT) participants.

Characteristic	Patients				Controls		
	Mean	SE	Range	Cut-off	Mean	SE	Range
Age (years)	32.80	1.69	25-49		35.80	2.28	25-53
SAPS	26.67	4.17	0-170				
SANS	48.09	4.56	0-125				
PAS	26.36	2.26	0-61	> 18			
SAS	19.00	1.74	0-40	> 12			
Simpson-Angus Scale	0.36	0.04	0-4	> 0.65			

Duration of illness (years)	11.23	1.30	2-24
Age at first psychosis	22.69	0.66	19-28
Number of hospitalizations	3.83	0.38	2-7
Dose of typical and atypical antipsychotics	32.85	4.93	
Dose of atypical antipsychotics	24.84	4.00	
Dose of typical antipsychotics	8.01	1.48	

Drugs are expressed as the cumulative value measured in dose-years in the form of (chlorpromazine equivalent in mg) × (time on dose measured in years) (Andreasen et al., 2010).

Stimuli

Two professional actors (one male and one female) were used for stimuli preparation. Stimuli consisted of 2-second colored video clips showing positive (laugh), negative (cry) and neutral (control) emotions. The neutral video clips showed actors making various faces (i.e., "making a face") that did not imply any particular emotional content, just that the actors were adopting some specific facial expressions. Actors when performed neutral stimuli always associated the making a face with specific vocalizations. Actors' full face was presented against a grey background. Stimuli consisted of actors' Laugh (Positive), Cry (Negative) and Control (Neutral) accompanied by the simultaneously produced sound of laughter, crying and a non emotional sound, respectively. Half of the stimuli was performed by the male actor, whereas the other half was performed by the female actress. Stimuli were recorded using a digital camera (25 frames/s, 720×576 pixels), with audio digitally recorded at 44.1 kHz. Stimuli were divided into four presentation modalities: Visual only, Audio only, Audio-Visual congruent and Audio-Visual incongruent. Every presentation modality was made of 60 stimuli [24 Laugh (Positive) stimuli, 24 Cry (Negative) stimuli and 12 Control (Neutral) stimuli]. In the Audio modality (A), the sound of the video clips of laugh, cry and control stimuli was extracted from the original video clips and presented alone. In the Video modality (V), only the visual component of video-clips was presented, devoid of any sound. In the Audio-Visual

Congruent modality (AVC), the original video clips were presented with both modalities. In the Incongruent Audio-Visual modality (AVI), the video of a given expression was coupled and presented with the audio pertaining to a different video clip performed by the same actor (e.g. audio of laugh with the video of cry, audio of cry with the video of laughs and audio of a given neutral sound with the video of another neutral stimulus). Consequently, in AVI Laugh participants saw an actor crying but heard laughing, in AVI Cry participants saw an actor laughing but heard crying, and in Control condition they saw an actor making an unemotional face while hearing the sound of a different neutral stimulus.

Experimental procedure

Participants were individually tested in a sound attenuated laboratory room. They were invited to sit on a comfortable chair in front of a 19-inch computer monitor used for stimuli presentation, located at a distance of 70 cm. Audio tracks were presented at a comfortable sound level (<70 dB) through loudspeakers integrated in the computer monitor. Before starting, participants were invited to relax and refrain from moving during the experiment. Participants were instructed to carefully listen to and/or watch audiovisual stimuli. After exposure to each stimulus, participants were required to verbally rate how much positive or negative the stimulus was perceived on a scale from -3 (very negative) to +3 (very positive), where 0 indicated lack of perceived emotional content.

The experiment consisted of four experimental blocks of 60 stimuli each presented in randomized order. Each block consisted of one of the four modalities: Audio-Visual Congruent (AVC), Audio-Visual Incongruent (AVI), Audio (A) and Video (V). In every modality three emotional stimuli were presented in randomized sequence: Laugh (Positive), Cry (Negative) and Control (Neutral). A pause was provided at the end of each condition. The order of blocks was counterbalanced among participants. Each trial (Fig. 1) started with a fixation cross (the "+" symbol) presented for 1000ms (baseline), immediately followed by the stimulus, which lasted

2000ms, then followed by a question mark (the "?" symbol). After question mark presentation, participants verbally scored the emotional valence of each stimuli. The experimenter took note of participants' response in a record sheet and then started manually the next trial. The total duration of the experiment was about 40 minutes.
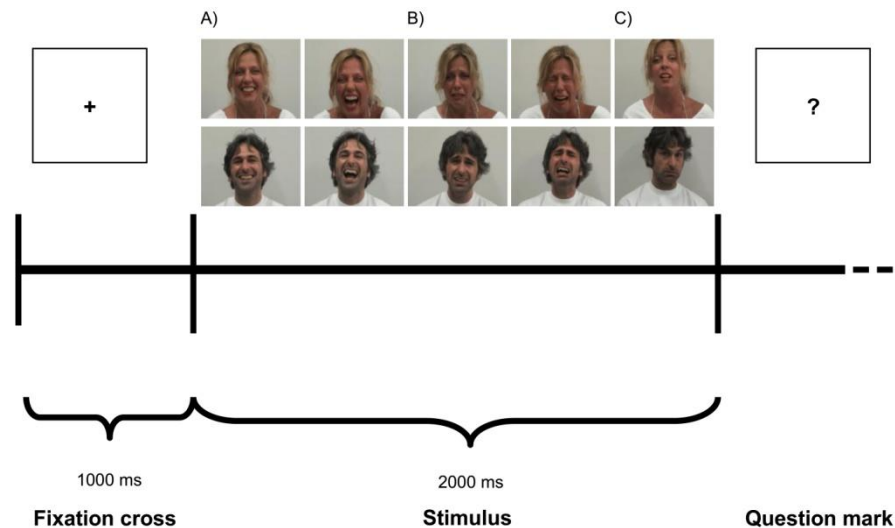

Figure 1. Experimental paradigm. Photographs illustrate examples of stimuli depicting Laugh (A), Cry (B) and Control (C).

EMG recording

To measure facial muscle activity, Ag/AgCl surface electrodes (diameter 3 mm) were attached bipolarly over the left (Dimberg and Petterson, 2000) *Zygomaticus major* and the *Corrugator supercilii* muscle regions (Friedlund and Cacioppo, 1986). In order to reduce the inter-electrode impedance, the participants' skin was cleaned with alcohol and rubbed with the electrode paste. Continuous electromyography (EMG) recordings from both muscles were simultaneously acquired with a CED Micro 1401 analog-to-digital converting unit (Cambridge Electronic Design, Cambridge, UK). The EMG signal was amplified (3000×), digitized (sampling rate: 2,5 kHz) and stored on a computer for offline analysis.

Data and Statistical Analysis

Behavioral Rating

The rating score of each participant was averaged on the basis of modality and emotion. The corresponding averaged rating scores were entered into a 4 (Modality: AVC, AVI, A, V) × 3 (Emotion: Laugh, Cry, Control) × 2 (Group: SZP and CNT) repeated measures ANOVA, with Modality and Emotion as within-participants factors and Group as between-participants factor.

EMG data analysis

Offline, data were submitted to a 50-500Hz band-pass filter to reduce movement related artifacts and environmental noise, and full-wave rectified. Data were then visually inspected, and data with remaining artifacts were excluded from subsequent analysis (mean percentage of discarded trails: 14.1% for CNT, 12.6% for SZP; T-test performed did not show significant differences between groups $t_{30} = 0.5$, $p > 0.6$). In accordance with earlier experiments (e.g., Dimberg et al., 2000), any distinct muscle response to the stimuli was expected to be detectable after 500ms of exposure. Thus, for each participant and trial, the averaged EMG responses of the two muscles were subdivided in 4 time periods (T1-T4) of 500ms each. Each time-bin was then normalized with respect to baseline (i.e., averaged pre-stimulus signal activity lasting 500ms: from 250 to 750ms of the 1000ms total duration of the baseline). Thus, an EMG normalized value above the 100% means an activation of a given muscle with respect to the baseline, whereas an EMG normalized value below the 100% indicate a relaxation of that muscle with respect to the baseline. In order to compare baselines, we performed two ANOVAs, one for each muscle, in which baselines raw data were compared, with Modality (AVC, AVI, A, V) as within-participants factor and Group (SZP, CNT) as between-participants factor. Mean EMG responses were then calculated for each Modality (AVC, AVI, A, V), Emotion (Laugh, Cry, Control) and Period (T1, T2, T3, T4). EMG data were entered into a 4 (Modality: AVC, AVI, A, V) × 3 (Emotion: Laugh, Cry, Control) × 4 (Period: T1: 0-500ms, T2: 500-1000ms, T3: 1000-1500ms, T4: 1500-2000ms) repeated measures ANOVA, with

Modality, Emotion and Period as the within-participants factors and Group (SZP and CNT) as between-participants factor. One separated ANOVA was conducted for each muscle (Corrugator and Zygomaticus).

Functional relation between EMG and Behavioral Rating

In order to investigate functional relations between the recorded EMG responses and behavioral rating, we calculated median EMG responses, separately for each group and for each emotion (positive, negative), irrespective of modalities and periods. We excluded from this analysis Control stimuli because they did not evoke any significant EMG response in both muscles (see Results). Regarding positive emotions, we considered for this analysis the following modalities in which we measured (see Results) Zygomaticus muscle activation: AVI Cry, AVC Laugh, A Laugh and V Laugh. Regarding negative emotions, we considered the following modalities in which we measured (see Results) Corrugator muscle activation: AVI Laugh, AVC Cry, A Cry and V Cry.

For each participant, we calculated the median EMG response for each emotion (positive, negative). If this value was equal or greater than the median value calculated separately for positive and negative emotions for the group the participant belonged to, we classified this participant as Externalizer. If, instead, this value was smaller than the median value calculated separately for positive and negative emotions for the group the participant belonged to, we classified this participant as Internalizer (see Kring and Gordon, 1998). Following this procedure, in the CNT group we obtained the median value of 95.14% (8 Externalizers and 7 Internalizers) for positive emotions and the median value of 99.24% (8 Externalizers and 7 Internalizers) for negative emotions. In the SZP group we obtained the median value of 95.15% (6 Externalizers and 9 Internalizers) for positive emotions and the median value of 100% (6 Externalizers and 9 Internalizers) for negative emotions. The corresponding averaged rating scores were entered into a 4 (Modality: AVC, AVI, A, V) × 2 (Group: SZP and CNT) repeated-measures ANOVAs, with Modality as within-participants factor and Group as between-participants factor. Overall, we ran

totally 4 ANOVAs, two in order to analyze behavioral data of the Externalizer cohort (one for each emotion valence: positive, negative) and two in order to analyze behavioral data of the Internalizer cohort (one for each emotion valence: positive, negative).

For all performed analyses, the significance level was set at p<0.05. Post-hoc comparisons (LSD Fisher test) were applied on all significant main factors and interactions.

2.3 Results

Behavioral Results

Results of the repeated-measures ANOVA performed on behavioral rating scores showed that the factor Emotion was significant ($F_{2,56}=222.52$ p<0.000). Post-hoc comparisons showed that Cry was rated by both groups more negative than Laugh and Control stimuli were considered without any emotional content (all p_s<0.000). Complementing this finding, the interaction between Emotion and Modality ($F_{6,168}=156.7$ p<0.000) was also significant (Fig. 2). This interaction was due to the fact that the negative rating scores reported for Laugh stimuli during the AVI modality (in which participants saw cry and heard laugh) differed from the positive rating scores reported for Laugh stimuli in all other modalities (all p_s<0.000). Similarly, the positive rating scores reported for Cry stimuli during the AVI modality (in which participants saw laugh and heard cry) significantly differed from the negative rating scores reported for Cry stimuli in all other modalities (all p_s<0.000). These differences in rating of AVI modality were due to the fact that both groups based their ratings on the emotion they saw (Laugh in AVI Cry and Cry in AVI Laugh), instead of the emotion they heard. Post-hoc analysis also showed that Control stimuli were rated as devoid of emotional content in all modalities by both groups (all p_s<0.000). Furthermore, with Laugh stimuli, V modality was rated more positive than A modality (p<0.05).
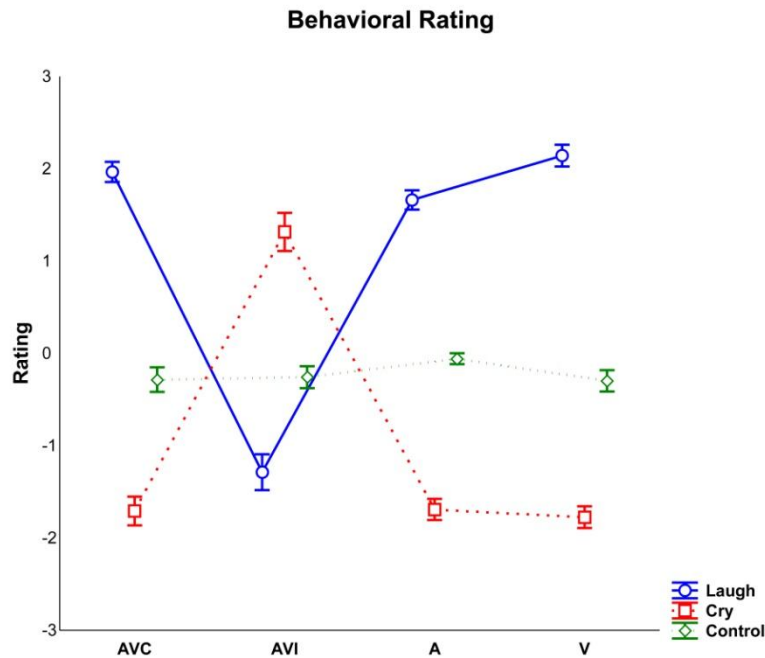
Behavioral Rating

Figure 2. Averaged rating scores detected for each modality (AVC: Audio-Video Congruent, AVI: Audio-Video Incongruent; A: Audio, V: Video) and emotion (Laugh, Cry, Control). Error bars represent standard errors of mean (SE).

Results also showed a significant interaction Emotion by Group ($F_{2,56}=3.43$ $p<0.05$). However, post-hoc analyses revealed no significant differences between groups (all $p_s >0.3$).

EMG Results

Two repeated measure ANOVAs, one for each muscle (Corrugator, Zygomaticus), were performed in order to compare baselines between the two groups, with Modality (AVC, AVI, A, V) as within-participants factor and Group (SZP, CNT) as between-participants factor. We found no significant main effect and interactions (all $p_s>0.05$). These results show that the baselines were not significantly different between the two groups.

Two repeated measures ANOVAs were performed in order to assess *Zygomatic Major* and *Corrugator Supercilii* EMG responses during the presentation of the stimuli of positive, negative

and neutral facial expressions and/or related sounds in four different modalities (AVC, AVI, A, V) (See Figs. 3 and 4).

Zygomaticus Major muscle

The analysis of *Zygomaticus Major* muscle EMG responses revealed a significant main effect of Emotion ($F_{2,56}=4.20$ p<0.05). Post-hoc showed that during the presentation of Laugh stimuli EMG responses were stronger than during the presentation of Control stimuli (p<0.01).

Furthermore, the interaction Modality by Emotion was also significant ($F_{6,168}=4.55$ p<0.001). Post-hoc showed that in AVI Cry condition (in which participants saw an actor laughing but heard crying) EMG Zygomaticus responses were stronger with respect to A cry and V cry (p<0.05). In AVI Laugh condition (in which participants saw instead an actor crying but heard laughing), EMG Zygomaticus responses were weaker than to all other conditions (i.e., AVC laugh, A laugh and V laugh) (p<0.01). In sum, results showed that EMG Zygomaticus responses in AVI modality were driven by what participants saw and not by what they heard. Furthermore, post-hoc analysis revealed that EMG responses were not modulated in all different modalities by Control stimuli presentation (all $p_s>0.05$). The interaction Emotion by Period was also significant ($F_{6,168}=2.82$ p<0.05). Post-hoc comparisons showed that during Laugh stimuli presentation Zygomatic EMG responses increased with time (T1 vs. T3 p<0.01, T1 vs. T4 p<0.0001, T2 vs. T4 p<0.01), whereas no modulation through time periods was found during Cry and Control stimuli presentation (all $p_s>0.05$).

The interaction Modality by Emotion by Period was also significant ($F_{18,504}=3.19$ p<0.0001). Of most interest, a significant interaction of all factors was observed among Modality, Emotion, Period and Group ($F_{18,504}=1.68$ p<0.05) (Fig. 3). Since Control stimuli were rated by both groups (SZP, CNT) as neutral and EMG activity was not modulated during perception of these stimuli (all $p_s>0.1$), we can considered them as effective neutral stimuli for emotion perception. Thus, we

compared EMG Zygomaticus activity during the presentation of positive (Laugh) and negative (Cry) emotion-related stimuli with neutral (Control) stimuli.

In line with previous literature (Dimberg and Thumberg, 1998), post-hoc comparisons revealed that CNT group showed Zygomaticus EMG responses when they saw and heard actors laughing in a congruent way (i.e., AVC modality) 500ms after stimulus onset (T2, T3, T4; all p_s<0.000). By comparing EMG responses to positive and negative stimuli (Fig. 3a), we found an inhibition in the same temporal periods for the latter ones (T2, T3, T4; all p_s<0.000). During perception of positive stimuli SZP group showed significant EMG activation, occurring later, 1000ms after stimulus onset (T3, T4; all p_s<0.01). However, the same EMG responses were recorded during both positive and negative stimuli presentations (T3, T4; all p_s>0.8). We thus defined this EMG response as "non-specific activation", because it appeared independently of the perceived emotion (Laugh, Cry).

As shown in Fig. 3b, in CNT participants Zygomaticus EMG responses occurred when they saw actors laughing but they heard crying (i.e., AVI Cry condition, in which the visual and auditory components of the stimuli are combined in an incongruent way) 500ms after stimulus onset (T2, T3, T4; all p_s<0.05). By comparing EMG activity recorded during AVI Laugh condition with that recorded during AVI Cry condition, we found inhibition in the same time periods (T2, T3, T4 all p_s<0.001). In AVI condition, we thus observed that Zygomatic muscle activation was driven by what CNT saw and not by what they heard.

SZP participants did not activate Zygomatic muscle in this condition (all p_s>0.05). By contrasting EMG activity during AVI Laugh condition with that recorded during AVI Cry condition, inhibition was found (T2, T3, T4; all p_s<0.05). When emotional visual and auditory information contrasted, patients did not activate EMG Zygomaticus muscle.

As shown in Fig. 3c, in CNT group Zygomaticus EMG responses occurred when they only heard laughing (i.e., A modality) already at T1, that is, 500ms after stimulus onset (T1, T2, T3, T4;

all $p_s<0.05$). By comparing EMG activity recorded during Cry stimuli with that recorded during Laugh stimuli, inhibition during the same time periods was found (T1, T2, T3, T4; all $p_s<0.01$).

SZP participants did not activate Zygomatic muscle in this condition (all $p_s>0.4$). When positive emotional auditory information was presented alone, patients did not react with any Zygomatic EMG responses.

As shown in Fig. 3d, in CNT group Zygomaticus EMG responses occurred when they only saw laugh (i.e., V modality) already at T1, that is, 500ms after stimulus onset (T1, T2, T3, T4; all $p_s<0.05$). Still in V modality, by comparing EMG activity recorded during Cry stimuli with that recorded during Laugh stimuli, inhibition during the same time periods was found (T1, T2, T3, T4; all $p_s<0.05$).

In SZP group EMG activation occurred already at T1, that is, 500ms after stimulus onset (T1, T2, T3, T4; all $p_s<0.05$) during positive stimuli. However, no difference was found between EMG responses recorded during negative and positive stimuli, because, similarly to AVC modality, Zygomaticus responded also during negative stimuli presentation (T1, T2, T3, T4; all $p_s>0.05$). We define this EMG response as "non-specific activation", because it appeared independently of the perceived emotion (Laugh, Cry).
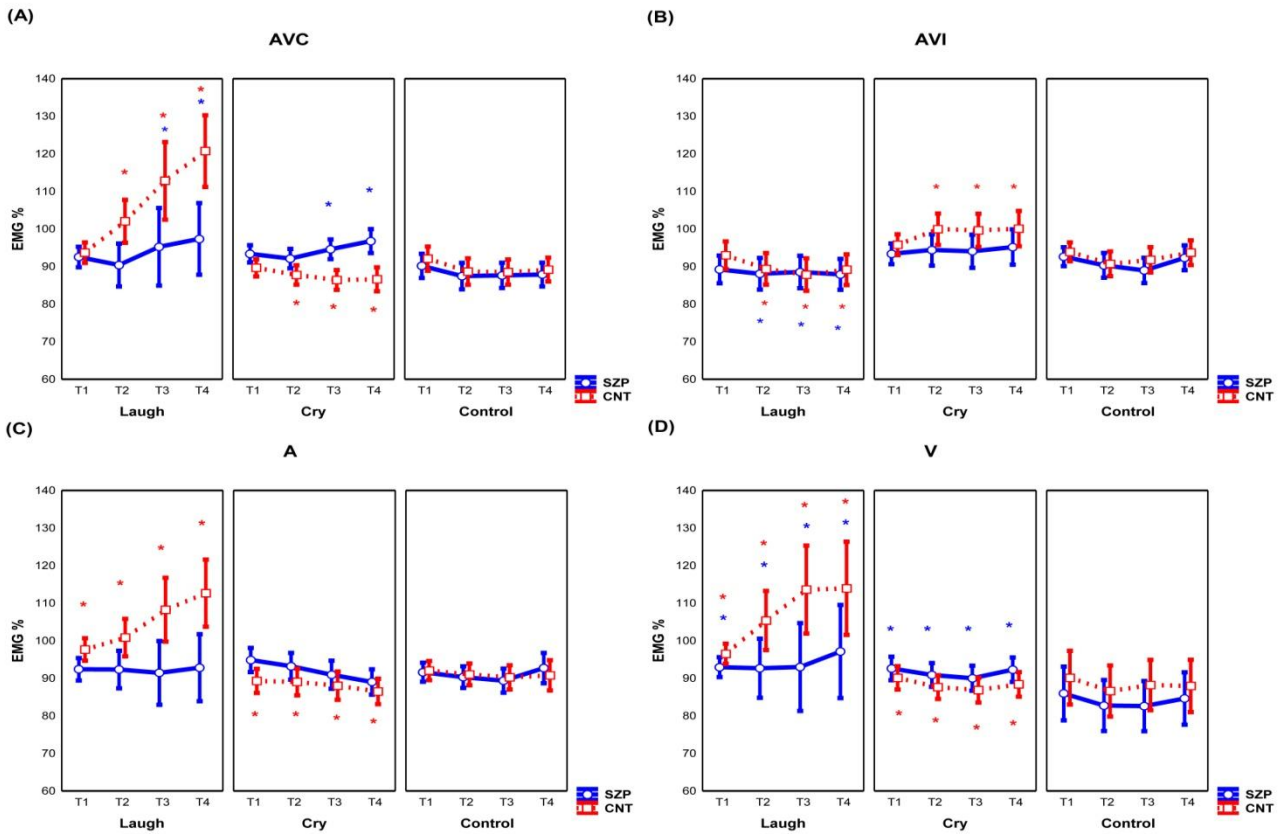
Zygomaticus Major

Figure 3. Mean EMG responses recorded for *Zygomaticus Major* muscle for each modality [AVC (Audio-Video Congruent) (A), AVI (Audio-Video Incongruent) (B), A (Audio) (C), and V (Video) (D)]. The significant differences are indicated by colored asterisks (red for CNT, blue for SZP). Asterisks located in the upper part of the panels indicated a significant activations with respect to Control stimuli; asterisks located in the lower part of the panels indicated significant differences between emotions. Y-axis: 100% represents the mean EMG response of the baseline. X-axis: Time Periods (T1: 0-500ms, T2: 500-1000ms, T3: 1000-1500ms, T4: 1500-2000ms). Error bars represent standard errors of mean (SE).

Corrugator Supercilii muscle

The analysis of *Corrugator Supercilii* muscle EMG responses revealed a significant interaction Modality by Emotion ($F_{6,168}=3.11$ p<0.01). Post-hoc showed that in AVI Cry condition (in which participants saw an actor laughing but heard crying) EMG Corrugator responses were weaker than in all other conditions (i.e., AVC cry, A cry and V cry) (p<0.05). In AVI Laugh condition (in which participants saw an actor crying but heard laughing), EMG Corrugator responses were stronger only with respect to the V laugh condition (p<0.05). Furthermore, post-hoc

analysis revealed that EMG responses were not modulated by different modalities during Control stimuli presentation (all $p_s > 0.7$).

Most interestingly, a significant interaction Modality by Emotion by Period was also observed ($F_{18,504} = 2.78$ $p < 0.001$) (Fig. 4). Since Control stimuli had been rated neutral by both groups (SZP, CNT) and EMG activity was never modulated during this condition (all $p_s > 0.2$), we considered Control stimuli, also for Corrugator EMG responses, as effective neutral stimuli for emotion perception. We performed the same comparisons already described for Zygomaticus muscle.

Post-hoc comparisons revealed that in both groups (SZP, CNT) Corrugator EMG responses occurred when they saw and heard cry (i.e., AVC modality) 500ms after stimulus onset (T2, T3, T4; all $p_s < 0.01$). Inhibition occurred during positive stimuli presentation in the same time periods (T2, T3, T4; all $p_s < 0.000$).

Both groups activated Corrugator muscle when they saw cry but they heard laugh (i.e., AVI Laugh modality) 1000ms after stimulus onset (T3 $p < 0.05$; T4 $p = 0.05$). By comparing EMG activity recorded during AVI Cry with that recorded during AVI Laugh, inhibition 500ms after stimulus onset was found (T2, T3, T4 all $p_s < 0.05$). In AVI modality, Corrugator muscle activation was driven by what both groups of participants saw and not by what they heard.

Corrugator EMG responses occurred when both groups heard cry (i.e., A modality) 500ms after stimulus onset (T2, T3, T4; all $p_s < 0.01$), as it happened in AVC modality. EMG activity was inhibited during presentation of Laugh stimuli in the same time periods (T2, T3, T4; all $p_s < 0.0001$).

Corrugator EMG responses occurred when both groups saw cry (i.e., V modality) 500ms after stimulus onset (T2, T3, T4; all $p_s = 0.0000$), as in AVC and A modalities. EMG activity was inhibited during presentation of Laugh stimuli in the same time periods (T2, T3, T4; all $p_s < 0.000$).

For Corrugator muscle, we found no significant main effects and interactions of Group factor (all $p_s > 0.05$).

41

Corrugator Supercilii
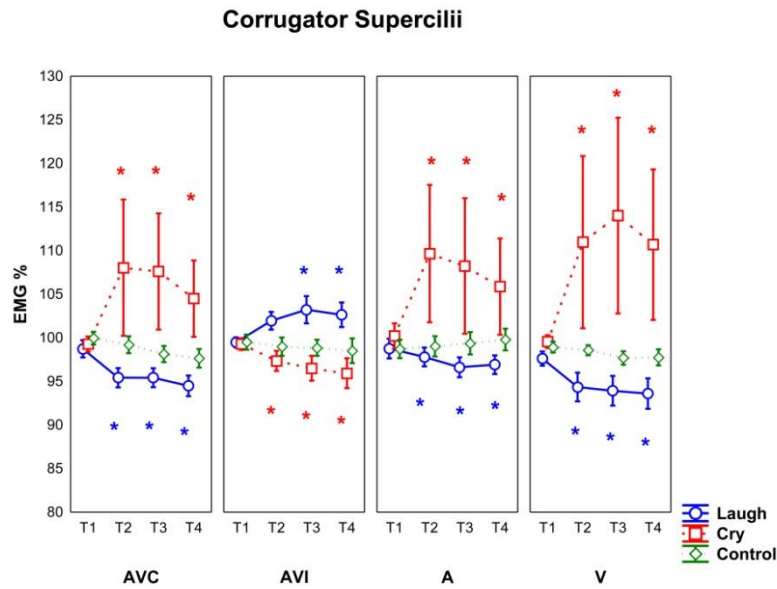
Figure 4. Mean EMG responses recorded for *Corrugator Supercilii* muscle for all participants (SZP, CNT). All other conventions as in Figure 3.

Functional relations between EMG and behavioral rating

In order to analyze behavioral data of the Externalizer and Internalizer cohorts, each of which comprised patients and control participants, two ANOVAs for each cohort (one for each emotion: positive, negative) were run.

Externalizer cohorts

For both the Externalizer cohorts, no significant Group main effects and interactions were found for positive emotions (all $p_s > 0.8$) as well as for negative emotions (all $p_s > 0.8$). For positive emotions, only a significant main effect of Modality ($F_{3,42} = 5.13$ $p < 0.01$) was found. Since no other significant main effects and interactions were found, this means that participants belonging to the Externalizer cohorts, more responding with congruent facial mimicry to positive and negative emotions, also gave correct behavioral ratings, with no differences between groups.

Internalizer cohorts

Regarding the results of the ANOVA performed on the Internalizer cohort for positive emotions, we found a significant main effect of Group ($F_{1,12}=7.40$ $p<0.05$). Post-hoc comparisons revealed that CNT group gave more positive ratings than SZP group ($p<0.05$). The factor Modality was also significant ($F_{3,36}=4.77$ $p<0.01$) and AVI modality received lower ratings with respect to AVC and V modalities ($p_s<0.01$).

Regarding the results of the ANOVA performed on the Internalizer cohort for negative emotions we found, again, a significant main effect of Group ($F_{1,12}=5.63$ $p<0.05$). Post-hoc comparisons revealed that CNT group gave more negative ratings than SZP group ($p<0.05$). The factor Modality was also significant ($F_{3,36}=4.44$ $p<0.01$), and AVI modality received the most positive ratings with respect to all other modalities ($p_s<0.05$).

The Internalizer cohort had EMG below the 100% (i.e., below the baseline value), therefore those participants did not activate their muscles in response to emotional stimuli. Within the Internalizer cohort, we found a significant difference between CNT and SZP groups both for positive and negative emotions. Interestingly, SZP group gave more neutral ratings to perceived positive and negative emotions (see Fig. 5).
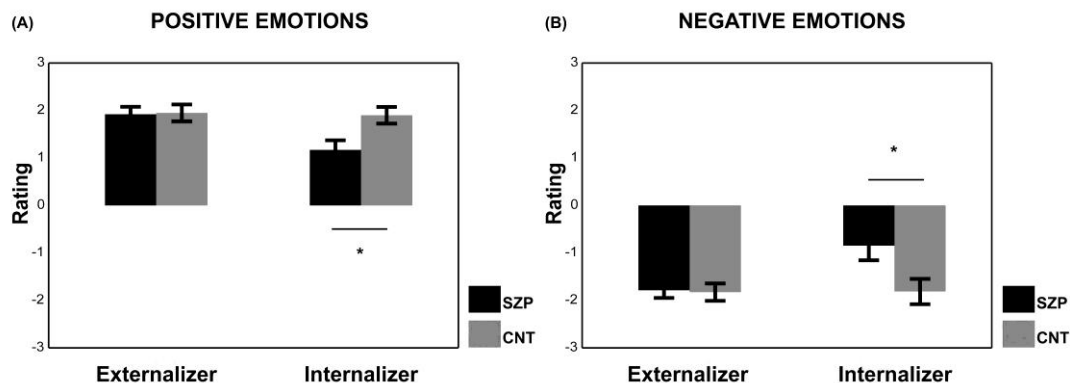

Figure 5. Mean rating scores of Externalizer and Internalizer cohorts during the presentation of Positive (A) and Negative (B) emotions. Asterisks represent significant differences between SZP and CNT. All other conventions as in Figure 3.

2.4 Discussion

Our study shows that SZP and CNT participants adequately recognized the emotional quality of the stimuli in all modalities: both groups judged Laugh as positive emotion, Cry as negative emotion and Control stimuli as devoid of any emotional content. Similarly, they were able to score dimensionally the perceived emotions (Laugh, Cry, Control) and, in AVI condition, both groups privileged the visual over the auditory modality. Indeed, they judged the emotion they saw rather than the emotion they heard.

With respect to EMG recordings, CNT group results are coherent with previous studies (Dimberg and Thumberg, 1998) that documented the role of Zygomaticus muscle in response to positive emotional stimuli and that of Corrugator Supercilii in response to negative ones. Also the timing of the activation of the muscles was in line with previous studies (500ms after stimulus onset). However, with "single modalities" (A and V) intense EMG responses of Zygomaticus muscle were evoked by positive emotions even before 500ms from stimulus onset. Notably, the inclusion of Control stimuli enriched the experimental paradigm with an effective neutral stimulus, which proved to evoke no EMG response and be judged by all participants as emotionally neutral. This shows that facial mimicry does not occur indiscriminately whenever one looks at the moving face of someone else, but requires the observation of emotion-specific pattern of facial movements. The same emotional specificity of EMG activation also occurred in Audio modality where only Laugh and Cry sounds were able to evoke EMG activation of the Zygomaticus and Corrugator muscles, respectively.

A further innovative feature of the adopted paradigm was the Incongruent (AVI) condition. Interestingly enough, we discovered that in AVI condition healthy participants reacted with rapid and automatic mimicry following the visual emotional content of the stimuli, while disregarding the auditory expressed contrasting emotion.

44

Whereas CNT and SZP groups reacted to negative emotional stimuli in the same way, SZP participants did not respond or showed inadequate EMG reactions (a "non-specific response") to positive emotions. Indeed, in AVI and Audio modalities no EMG activation was found, whereas in AVC and V modalities a non-specific response appeared independently of the perceived emotion (Laugh, Cry).

In our study, we found that CNT and SZP groups similarly reacted with EMG corrugator responses to negative emotional stimuli. Notably, our findings regarding patients' motor resonance in response to negative stimuli cohere with previous qualitative and quantitative studies documenting how everyday life of patients suffering from schizophrenia is marked by selective biases towards negative emotional experiences which amplify stress-vulnerability and are possibly fostered by persecutory feelings, increased impressionability and oversensitivity to perceived threats. This might be interpreted in line with Kapur's concept of *aberrant salience,* which posits that positive symptoms of schizophrenia may arise out of "the aberrant assignment of salience to external objects and internal representations" (Kapur 2003; Van Os and Kapur, 2009). Hence patients´ emotional susceptibility to negative stimuli, resulting in their persistent negative attitude in everyday life might act as a self-perpetuating mechanism of disturbed salience (Mattes et al., 1995; Kring and Earnst, 1999). Thus, positive daily experiences are few and the occasions of showing congruent motor resonance with happy emotions could be consequently uncommon in patients suffering from schizophrenia (Kring and Earnst, 2003; Wolf et al., 2004; 2006; Trèmeau, 2006), hence the lack of specific and congruent responses of Zygomaticus muscle to positive stimuli.

According to previous studies (Kring and Neale, 1996; Sison et al., 1996; Aghevli et al., 2003), patients diagnosed with schizophrenia also show a disjunction between the expression and the behavioral rating of emotions. In the present study we found this dissociation only for positive emotions, where normal emotional rating was not accompanied by congruent EMG responses.

However, by dichotomizing both groups of participants in two cohorts (Externalizers and Internalizers, Kring and Gordon, 1998) according to the intensity of their EMG congruent

responses, we found that the patients' cohort of Internalizers gave more neutral ratings with respect to control group. This means that in patients facial mimicry in response to positive and negative emotions is crucial to correctly judge from a dimensional point of view the perceived emotion. These data cohere with previous findings documenting empathic response deficits in Schizophrenia (Varcin et al., 2010; Dernt et al., 2009) that may be related with abnormalities in the mirror neurons mechanisms. According to this model, involuntary facial mimicry constitutes an important low-level mechanism contributing to the experience of empathy (for a review, see Singer and Lamm, 2009), *via* processes of simulation and perception-action coupling subserved by activation of the mirror neurons mechanism. In other words, involuntary facial mimicry reflects an embodied simulation of the perceived emotion, which facilitates its understanding (Gallese, 2003; 2005; 2006; Halberstadt et al., 2009; Niedenthal, 2007; Niedenthal et al., 2009) by promoting primary empathic resonance on a bodily level (Gallese, 2001; Oberman et al., 2007; Preston and De Waal, 2002; Sonnby-Borgstrom 2002; Sonnby-Borgstrom et al., 2003). Hence, the disruption of this low-level mechanism may contribute to the well known empathy deficits in schizophrenia (Varcin et al., 2010). Along similar lines, Dimberg et al. (2011) demonstrated that the ability to react with facial EMG activations to facial expressions and to rate these stimuli as more intense is particularly evident among people with high emotional empathy. Our findings cohere with those of Dimberg et al. (2011), since Internalizer patients neither react with any EMG response, nor rated positive or negative emotional stimuli as significantly more intense.

It should be added that Internalizer healthy participants could correctly score perceived emotions despite their apparent EMG hyporeactivity. This result shows that multi-modal emotion recognition can occur even without full-blown facial mimicry. This might be due to the recruitment of high-level cognitive mechanisms possibly fostered through coping strategies. Facial mimicry might be a necessary condition *for fine-grained emotional evaluation* only for Internalizer patients, who are impaired in correctly judging the intensity of positive and negative emotions.

The interpretation of the current findings, however, should be tempered by some limitations. First, the relatively modest sample size reduced the statistical power. Hence possible group differences, such as regarding the EMG corrugator response to negative stimuli, might not have been detected. Second, all participants with schizophrenia were under antipsychotic medications, which might act as a confounders in EMG responses. Nonetheless, since the participants' SAS score (a specific psychometric index sensitive to neuroleptic-induced parkinsonism) was below the cut-off, we are inclined to consider minimal such potential confounder.

It might also be worth noting, that group differences in EMG activation could not be attributed to attentional or motivational factors, for three main reasons. First, all patients were clinically stable (i.e., without hallucinations and similarly flamboyant psychopathology) when underwent the current experiment. Second, the ratings show that both groups correctly scored the different emotions without significant inter-group differences. Third, the lack of responses that characterized patients was emotion specific, was present only in two modalities, and it was not casually distributed among conditions.

In conclusion, this study provides new evidence on the emotion-specificity of facial mimicry. Furthermore, it demonstrates that (1) congruent facial mimicry can be evoked multi-modally and that (2) when Video and Audio modalities are incongruently associated, the Video modality prevails on the Audio as a response-trigger. The paradigm also proved sensitive to detect deficits in rapid facial mimicry for positive emotions in patients diagnosed with schizophrenia. We interpreted such deficits in rapid facial mimicry as indicative of a possible low-level impairment of motor resonance mechanisms, which may explain a portion of the empathizing deficits in schizophrenia. This coheres with our finding that the weaker facial mimicry response shown by patients' Internalizer cohort is related to difficulties in correctly judging the intensity of positive and negative emotions.

In our view, these findings could lead to future studies on the nature of emotional deficits in Schizophrenia, capitalizing on the convergence between neuroscience and psychopathology. Indeed, contemporary psychopathological research emphasizes the relevance of disruption of

implicit bodily functioning (of which facial mimicry is a crucial component) for the loss of practical immersion in the intersubjective world that constitutes the hallmark of schizophrenia spectrum vulnerability (see Parnas et al. 2002; Parnas, 2011; Fuchs 2005; Stanghellini 2004; see also Ferri et al. 2012; Ebisch et al. 2012; Gallese and Ferri, 2013). Therefore, the disturbance of motor resonance revealed in this study, might be implicated in some of the disorders of intersubjective attunement that phenomenologically-oriented psychopathology indicates as core features of Schizophrenia (Minkowski, 1927; Blankenburg, 1971; Parnas and Bovet, 1991; Parnas et al., 2002).

The interpretation of these results grounded on the hypothesis of an impaired functionality of motor resonance mechanisms in patients diagnosed with schizophrenia, should be limited by the lack in our study of direct measures of the entailed underpinning neural mechanisms. Nevertheless, a previous fMRI study carried out by Carr et al. (2003), demonstrated that in healthy participants observation and imitation of emotions activated a similar neural network of brain areas, in which the insula acted as an interface between the premotor component of the mirror mechanism and the limbic system, thus enabling the translation of an observed or imitated facial emotional expression into its internally felt emotional significance. Such results were interpreted by the authors as a mechanism that may mediate the understanding of the emotional state of others, thus contributing to empathy.

Overall, our results provide an encouraging exploratory paradigm to investigate the nature of emotional deficits in Schizophrenia that could be fruitfully coupled with neuroimaging studies aimed to investigate the neural substrate underpinning the deficits in rapid facial mimicry in patients suffering from schizophrenia.

References

Adelmann, P. K., and Zajonc, R. B. (1989). Facial efference and experience of emotion. *Ann Rev Psychol.* 40, 249-280.

Aghevli, M. A., Blanchard, J. J., and Horan, W. P. (2003). The expression and experience of emotion in schizophrenia: a study of social interactions. *Psychiatry Res.* 119, 261-270.

Andreasen, N. C. (1984a). *Scale for the Assessment of Negative Symptoms (SANS).* Iowa City: University of Iowa.

Andreasen, N. C. (1984b). *Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City: University of Iowa.

Andreasen, N. C., Pressler, M., Nopoulos, P., Miller, D., and Ho, B. C. (2010). Antipsychotic Dose Equivalents and Dose-Years: A Standardized Method for Comparing Exposure to Different Drugs. *Biol Psychiatry* 67, 255–262.

Berenbaum, H., and Oltmanns, T. F. (1992). Emotional experience and expression in schizophrenia and depression. *J Abnorm Psychol.* 101, 37-44.

Blankenburg, W. (1971). *Der Verlust der natürlichen Selbstverständlichkeit. Ein Beitrag zur Psychopathologie symptomarmer Schizophrenien.* Stuttgart: Enke.

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias.* Oxford, England: International Universities Press. (Original work published in 1911).

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., and Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A.* 100, 5497–5502 .

Chapman, L. J., Chapman, J. P., and Raulin, M. L. (1976). Scales for Physical and Social Anhedonia. *J Abnorm Psychol.* 85, 374-382.

Derntl, B., Finkelmeyer, A., Toygar, T. K., Hülsmann, A., Schneider, F., Falkenberg D. I., and Habel, U. (2009). Generalized deficit in all core components of empathy in schizophrenia. *Schizophr Res.* 108, 197-206.

Dimberg, U. (1982). Facial reactions to facial expressions. *Psychophysiology* 19, 643-647.

Dimberg, U. (1988). Facial electromyography and the experience of emotion. *J Psychophysiology* 2, 277-282.

Dimberg, U., Andréasson, P., and Thumberg, M. (2011). Emotional empathy and facial reactions to facial expressions. *J Psychophysiol.* 25, 26-31.

Dimberg, U., and Petterson, M. (2000). Facial reactions to happy and angry facial expressions: Evidence for right hemisphere dominance. *Psychophysiology* 37, 693–696.

Dimberg, U., and Thumberg, M. (1998). Rapid facial reactions to emotional facial expressions. *Scand J Psychol.* 39, 39-45.

Dimberg, U., Thunberg, M., and Elmehed, K. (2000). Unconscious facial reactions to emotional facial expressions. *Psychol Sci.* 11, 86-89.

Dimberg, U., Thunberg, M., and Grunedal, S. (2002). Facial reactions to emotional stimuli: Automatically controlled emotional responses. *Cogn Emot.* 16, 449-471.

Earnst, K. S., Kring, A. M., Kadar, M. A., Salem, J. E., Shepard, D. A., and Loosen, P. T. (1996). Facial expression in schizophrenia. *Biol psychiatry* 40, 556-558.

Ebisch, S. J. H., Salone, A., Ferri, F., De Berardis, D., Mantini, D., Ferro, F. M., Romani, G. L., and Gallese, V. (2012). Out of touch with reality? Social perception in first episode schizophrenia. Soc Cogn Affect Neurosci. doi:10.1093/scan/nss012.

Ekman, P., and Oster, H. (1979). Facial expressions of emotion. *Annu Rev Psychol.* 30, 527–554.

Ferri, F., Frassinetti, F., Mastrangelo, F., Salone, A., Ferro, F. M., and Gallese, V. (2012). Bodily self and schizophrenia: The loss of implicit self-body knowledge. *Consciousness Cogn*. 21, 1365-1374.

Fridlund, A. J., and Cacioppo, J. T. (1986). Guidelines for human electromyographic research. *Phsychophysiology* 23, 567-589.

Fuchs, T. (2005). Corporealized and Disembodied Minds: A Phenomenological View of the Body in Melancholia and Schizophrenia. *Philos Psychiat Psychol.* 12, 95-107.

Gallese, V. (2001). The 'shared manifold' hypothesis: From mirror neurons to empathy. *J Consc Stud.* 8, 33-50.

Gallese, V. (2003). The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology* 36, 171-180.

Gallese, V. (2005). Embodied simulation: From neurons to phenomenal experience. *Phenomenol Cogn Sci.* 4, 23-48.

Gallese, V. (2006). Intentional attunement: A neurophysiological perspective on social cognition and its disruption in autism. *Brain Res.* 1079, 15-24.

Gallese, V. and Ferri, F. (2013). Jaspers, the body and Schizophrenia. The bodily self. *Psychopathology*, in press. [Epub ahead of print, 2013 Jul 17]. DOI: 10.1159/000353258].

Goldman, A. I., and Sripada, C. S. (2005). Simulationist models of face-based emotion recognition. *Cognition* 94, 193-213.

Halberstadt, J., Winkielman, P., Niedenthal. P. M., and Dalle, N. (2009). Emotional conception: how embodied emotion concepts guide perception and facial action. *Psychol Sci.* 20, 1254-1261.

Han, C., Park, G. Y., Wang, S. M., Lee, S. Y., Lee, S. J., Bahk, W. M., and Pae, C. U. (2012). Can botulinum toxin improve mood in depressed patients? *Expert Rev of Neurother.* 12, 1049-1051.

Heimann, H., and Spoerri, T. (1957). Das Ausdruckssyndrom der mimischen Düsintegrierung bei chronischen Schizophrenen. *Schweiz Med Wschrft*, 35/36, 1126-1132.

Iwase, M., Yamashita, K., Takahashi, K., Kajimoto, O., Shimizu, A., Nishikawa, T., Shinosaki, K., Sugita, Y., and Takeda, M. (1999). Diminished facial expression despite the existence of pleasant emotional experience in schizophrenia. *Methods Find Exp Clin Pharmacol.* 21, 189-194.

Janno, S., Holi, M. M., Tuisku, K., and Wahlbeck, K. (2005). Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. *BMC Neurol.* 5, 5.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 160, 13–23.

Kring, A. M., and Earnst, K. S. (1999). Stability of emotional responding in schizophrenia. *Behav Ther.* 30, 373-388.

Kring, A. M., and Earnst, K. S. (2003). "Nonverbal behavior in schizophrenia", in *Nonverbal Behavior in Clinical Settings*, eds. P. Philippot, E. Coats, and R. S. Feldman (New York: Oxford University Press), 263-286.

Kring, A.M., and Gordon, A. H. (1998). Sex differences in emotion: Expression, experience, and physiology. *J Pers Soc Psychol.* 74, 686-703.

Kring, A. M., Kerr, S. L., Smith, D. A., and Neale, J. M. (1993). Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. *J Abnorm Psychol.* 102, 507-517.

Kring A. M., and Neale, J. M. (1996). Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotions? *J Abnorm Psychol.* 105, 249-257.

Larsen, J. T., Norris, C. J., and Cacioppo, J. T. (2003). Effects of positive and negative affect on electromyographic activity over zygomaticus major and corrugator supercilii. *Psychophysiology* 40, 776-785.

Lundqvist, L. O., and Dimberg, U. (1995). Facial expressions are contagious. *J Psychophysiol.* 9, 203-211.

Mattes, R. M., Schneider, F., Heimann, H., and Birbaumer, N. (1995). Reduced emotional response in schizophrenic patients in remission during social interaction. *Schizophr Res.* 17, 249-255.

Minkowski, E. (1927). *La schizophrénie. Psychopathologie des schizoides et des schizophrènes*. Paris: Payot.

Niedenthal, P. M. (2007). Embodying emotion. *Science* 316, 1002-1005.

Niedenthal, P. M., Mermillod, M., Maringer, M., and Hess, U. (2010). The simulation of smiles (SIMS) model: embodied simulation and the meaning of facial expression. *Behav Brain Sci.* 33, 417–433.

Niedenthal, P. M., Winkielman, P., Mondillon, L., and Vermeulen, N. (2009). Embodiment of emotion concepts. *J Pers Soc Psychol.* 96, 1120-1136.

Oberman, L. M., Winkielman, P., and Ramachandran, V. S. (2007). Face to face: blocking facial mimicry can selectively impair recognition of emotional expressions. *Soc Neurosci.* 2, 167-78.

Parnas, J. (2011). A disappearing heritage: the clinical core of schizophrenia. *Schizophr Bull.* 37, 1121-1130.

Parnas, J., and Bovet, P. (1991). Autism in schizophrenia revisited. *Compr Psychiatry* 32, 7-21.

Parnas, J., Bovet, P., and Zahavi, D. (2002). Schizophrenic autism: Clinical phenomenology and pathogenetic implications. *World Psychiatry* 1, 131-136.

Phillips, L. K., and Seidman, L. J. (2008). Emotion Processing in Persons at Risk for Schizophrenia. *Schizophr Bull.* 34, 888-903.

Preston, S. D., and De Waal, F. B. M. (2002). Empathy: Its ultimate and proximate bases. *Behav Brain Sci.* 25, 1-20.

Rymarczyk, K., Biele, C., Grabowska, A., and Majczynski, H. (2011). EMG activity in response to static and dynamic facial expressions. *Int J Psychophysiol.* 79, 330-333.

Simpson G. M., and Angus, G. W. S. (1970). A rating scale for extrapyramidal side effects. *Acta Psych Scand.* 45, 11-19.

Singer T. and Lamm C. (2009). The social neuroscience of empathy. *Ann N Y Acad Sci.* 1156, 81-96.

Sison, C. E., Alpert, M., Fudge, R., and Stern, R. (1996). Constricted expressiveness and psychophysiological reactivity in schizophrenia. *J Nerv Ment Dis.* 184, 589-597.

Sonnby-Borgström, M. (2002). Automatic mimicry reactions as related to differences in emotional empathy. *Scand J Psychol.* 43, 433– 443.

Sonnby-Borgström, M., Jönsson, P., and Svensson, O. (2003). Emotional empathy as related to mimicry reactions at different levels of information processing. *J Nonverbal Behav.* 27, 3–23.

Stanghellini, G. (2004). *Disembodied Spirits and Deanimated Bodies: The Psychopathology of Common Sense.* Oxford: Oxford University Press.

Trèmeau, F. (2006). A review of emotion deficits in schizophrenia. *Dialogues Clin Neurosci.* 8, 59–70.

Van Os, J., and Kapur, S. (2009). Schizophrenia. *Lancet* 374, 635–645.

Varcin, K. J., Bailey, P. E., and Henry, J. D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. *J Int Neuropsychol Soc.* 16, 621-629.

Walker, E. F., Grimes, K. E., Davis, D. M., and Smith, A. J. (1993). Childhood precursors of schizophrenia: Facial expressions of emotion. *Am J Psychiatry* 150, 1654-1660.

Wolf, K., Mass, R., Kiefer, F., Eckert, K., Weinhold, N., Wiedemann, K., and Naber, D. (2004). The influence of olanzapine on facial expression of emotions in schizophrenia - an improved facial EMG study. *Germ J Psychiatry* 7, 14-19.

Wolf, K., Mass, R., Kiefer, F., Wiedemann, K., and Naber, D. (2006). Characterization of the facial expression of emotions in Schizophrenia Patients: preliminary findings with a new electromyography method. *Can J Psychiatry* 51, 335-341.

3. Mirroring the Self: testing neurophysiological correlates of disturbed self-experience in Schizophrenia spectrum

3.1 Introduction

In recent years, nonpsychotic anomalous subjective experience was found to be an essential clinical feature of Schizophrenia Spectrum (SzSp) disorders (Schultze-Lutter, 2009; Sass & Parnas, 2003).

Phenomenological research indicates that disturbance of the basic sense of self may be a core phenotypic marker of SzSp disorders. The notion of self-disorder (SD) refers to a disruption of the sense of ownership of the experience and agency of action, that is associated with a variety of anomalous subjective experiences. Those experiences, which include varieties of depersonalization, loss of common sense, fading grip on perceptual and situational meanings, disordered sense of identity and embodiment, are characterized by subtle, non-psychotic qualitative changes in the structure of subjectivity that mostly affect *the sense of self* (Sass & Parnas, 2003; Parnas & Handest, 2003).

Clinically, SDs encompass a broad range of phenomena. They include various disturbances in the stream of consciousness (e.g., thought interference), mild perceptual aberrations, anomalous bodily experiences (e.g., somatic depersonalization), lack of sense of immersion in the world (e.g., anhedonia, sense of vitality) and other disorders of self-consciousness. Those phenomena can be reliably explored through systematic checklists such as the Bonn Scale for the Assessment of Basic Symptoms (BSABS) and the Examination of Anomalous Self-experience (EASE) (Gross et al., 1992; Parnas et al., 2005).

Such anomalous subjective experiences antedate the onset of flamboyant psychosis (Parnas & Handest, 2003; Møller & Husby, 2000; Corcoran et al., 2003; Klosterkotter et al., 2001; Schultze-Lutter et al., 2010; Parnas et al., 1998; Parnas et al., 2005) and occur in various schizophrenia-related conditions (i.e., full-blown schizophrenia, prodromal/at risk mental states, schizotypy, and

genetically high-risk individuals) (Møller & Husby, 2000; Klosterkotter et al., 2001; Parnas et al., 1998; Parnas et al., 2005; Schultze-Lutter et al., 2007a; Schultze-Lutter et al., 2007b; Schultze-Lutter et al., 2007c; Parnas et al., 2003; Mass 2000; Chapman & Chapman, 1987; Catts et al., 2000; Parnas 2000; Handest & Parnas, 2005).

Particularly, phenomenological psychopathological research exploring *self-disorders* (SDs) highlights that SDs form an important phenotype for the characterization of Schizophrenia Spectrum (SzSp) disorders, both in clinical and in genetically high-risk populations (Parnas et al., 2005; Parnas et al., 2003; Handest & Parnas, 2005; Raballo et al., 2011; Wieneke et al., 1997; Maggini & Raballo, 2003; Maggini & Raballo, 2004; Raballo & Parnas, 2011). SDs are a subset of anomalous experience and include unstable or attenuated sense of self-presence, lack of basic sense of self-coincidence (identity), blurred self-demarcation, disturbance in the tacit fluidity of the field of awareness, hyper-reflexivity and difficulty in grasping familiar meanings (Sass & Parnas, 2003).

Moreover, empirical evidence that SD is a valuable trait phenotype for indexing genetic liability to SzSp, was provided by a recent study documenting a gradient-like pattern of SDs that parallels the levels of increasing subclinical expressivity of spectrum psychopathology (i.e., no mental illness, no mental illness with schizotypal traits, personality disorders not fulfilling other personality disorders and schizotypal personality disorder) in a non-clinical, genetically high risk population (Raballo & Parnas, 2011).

Up to now, however, little is known about the electrophysiological bodily correlates of SDs. This is particularly important given the marked gap between patients' complaints (that generally entail disturbing experiences) and the most preeminent schizophrenia etio-pathogenetic theories and therapeutic practices (which are by large postulated at a body-brain level of description and analysis). Until now, nobody has ever found a direct association between phenomenological experience (i.e., the *mind* level) and electrophysiological evidence (i.e., the *body* level) in schizophrenia disorder.

An effort coming from neurobiology research attempted to bridge these different levels of psychopathology analyses, developing an account of brain mechanisms of action, language and emotions and relating them to the mirror neurons mechanism (Gallese 2003; Arbib & Mundhenck, 2005). Recent findings show that we can understand other people's actions, intentions and emotions through a mirror mechanism that simulates the same actions directly in our brain, hence making us feeling the same actions or emotions we perceive in others (i.e., *embodied simulation* mechanism). A mirror mechanism has also been claimed for empathy, promoted through the medium of facial motor resonance of the perceived emotions and bodily sensations (Gallese 2001; 2003; Sonnby-Borgström 2002; Sonnby-Borgström et al., 2003). In this framework, the body acts as a tacitly felt "mirror" of the other, by eliciting a non-inferential process of empathic perception, as if other individuals' emotions inhabited our body. Recent findings strongly support an impairment of emotional resonance in patients with schizophrenia, likely rooting these deficits to abnormalities in mirror neurons mechanisms. Particularly, the disruption of the low-level mechanism of facial mimicry, that normally occurs when someone perceives an emotion, leads to a failure of the embodied simulation of that emotion in patients with schizophrenia (Derntl et al., 2009; Varcin et al., 2010; Sestito et al., 2013) compromising emotional empathy and understanding (Gallese, 2003; Gallese, 2005; Gallese, 2006; Niedenthal, 2007; Niedenthal et al., 2009).

A phenomenological account of the implicit functioning of the body in everyday perception and action, turns the notion of the physical body into a living medium of the individual's relation to the world. According to this view, subtle distortions of these embodied mediating processes would be a crucial feature of schizophrenia, which - indeed - has been phenomenologically reconceptualized by Thomas Fuchs as a disorder of *embodied intersubjectivity* (Fuchs, 2005). The aim of this study is to investigate if there is a direct connection between subjective experience as indexed by the BSABS scale, and motor facial mimicry in response to emotional stimuli, that has been successfully proved to be a mirror motor resonance *proxy* (Varcin et al., 2010; Carr et al., 2003). In order to do this, we employed a novel paradigm proved to be sensitive enough to evoke

multi-modally congruent facial mimicry (electrophysiologically measured by means of facial Electromyographic activity, EMG). This paradigm turned out to be able to detect deficits in facial mimicry in schizophrenia patients (Sestito et al., 2013).

3.2 Methods

Sample

The sample, recruited at the Psychiatry Section of Parma University Department of Neuroscience, included eighteen outpatients (thirteen males, five females, mean age 34.2 years SE ±1.6) diagnosed with a Schizophrenia Spectrum disorder (i.e. schizophrenia or schizotypal personality disorder) according to DSM-IV diagnostic criteria (American Psychiatric Association, 1994). All of them were clinically stable (i.e., with no current psychotic symptoms) at the time of the assessment.

General psychopathology was assessed with the Scales for the Assessment of Positive and Negative Symptoms (Andreasen, 1984a; 1984b). Disturbances of subjective experience were investigated through the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Gross et al., 1992). (see Supplementary Material section for details). All patients were screened to rule out any history of neurological and vascular disorders, alcohol or drugs abuse and mental retardation. Patients were receiving different antipsychotic medications, and to quantify them we obtained the cumulative measure of lifetime drugs exposure following the method adopted by Andreasen and colleagues (Andreasen et al., 2010). Demographic and psychopathological features of the sample are provided in Table 1.

Table 1. Demographic variables and psychopathological characteristics of Schizophrenia Spectrum sample (SzSp). Drugs are expressed as the cumulative value measured in dose-years in the form of (chlorpromazine equivalent in mg) × (time on dose measured in years) (Andreasen et al., 2010).

Characteristic	Mean	SE	Range
Age (years)	34.17	1.63	25-49
SAPS	23.12	3.83	0-170
SANS	47.41	4.12	0-125
BSABS	41.72	4.01	0-103
Lenght of illness (years)	11.19	1.17	2-24
Age at first psychosis	24.06	1.04	19-34
Number of hospitalizations	3.38	0.44	0-7
Dose of typical and atypical antipsychotics	26.31	4.74	
Dose of atypical antipsychotics	19.56	3.77	
Dose of typical antipsychotics	6.75	1.35	

Written informed consent was obtained from all participants before entering the study, after the treating clinician gave them an exhaustive explanation about the study. The Ethics Committee of the University of Parma approved the study, that was carried out according with the ethical standards of the Declaration of Helsinki.

Experimental paradigm: stimuli and procedure

The experimental paradigm, validated and detailed in a previous study (see Chapter 2, Sestito et al., 2013), consisted of the following procedure. Participants were presented with stimuli portraying positive (Laugh), negative (Cry) and neutral (Control) emotional stimuli in visual (i.e., Video), auditory (i.e., Audio) modalities in isolation, and congruently (i.e., Audio-Visual Congruent, AVC) or incongruently (i.e., Audio-Visual Incongruent, AVI) associated. Participants were requested to recognize and quantitatively rate the emotional value of the perceived stimuli, while EMG activity of *Corrugator Supercilii* and *Zygomaticus Major* muscles was recorded. For

further details about stimuli, experimental procedure and EMG recording, please refer to Sestito and colleagues' (2013).

The BSABS interview

Disturbances of subjective experience were investigated through the Bonn Scale for the Assessment of Basic Symptoms (BSABS), Italian version (Gross et al., 1992). The BSABS is a 98 items semi-structured interview measuring subjective unusual experiences (i.e., Basic Symptoms), described in a prototypical manner (i.e., briefly defined and illustrated by examples of typical self-descriptions, supplemented by differential-diagnostic guidelines, question examples and suggestions of probes). The interview is divided into sections comprising five main phenomenological areas:

A) Dynamic Deficits with Direct Minus Symptoms: include complaints about increased physical and mental exhaustion and decreased energy, resilience and perseverance.

B) Dynamic Deficits with Indirect Minus Symptoms: comprise inner disquiet or tension, obsessive thought patterns, lack of concentration provoked by physical or mental strain. Patients try to avoid situations such as conversations and activities requiring close attention/additional demands. Other items of this category include increased impressionability by everyday events that are experienced more frequently and intrusively as exhausting, disparaging or offending.

C) Cognitive Thought, Perception and Movement Disturbances: encompass several disturbances involving thought management and control, qualitative and quantitative changes in perceptual experience, altered motor and automatic skills.

D) Cenesthesias: bodily unpleasant sensations which are idiosyncratically experienced as new and unusual (e.g., such as "Unusual bodily sensations of numbness and stiffness", "Migrating bodily sensations wandering through the body", "Kinesthetic sensations, pseudo-movements of the body").

E) Central Vegetative Disturbances: include several vague and widespread disturbances connected with neurovegetative parasympathetic and orthosympathetic activation as perceived by the patient in terms of disturbed vasomotor and thermoregulatory function.

Each item was scored as absent or present. The average interview duration was approximately 2-3 hours, and the referring clinicians were unaware of the study purpose.

Data analysis

Participants' behavioral rating scores and EMG data were analyzed following the same method used in the previous work (Sestito et al., 2013).

Behavioral Rating

The rating scores of each participant were averaged on the basis of modality and emotion and were entered into a 4 (Modality: AVC, AVI, Audio, Video) × 3 (Emotion: Laugh, Cry, Control) repeated measures ANOVA, with Modality and Emotion as within-participants factors.

Facial EMG data reduction and analysis

Offline, data were band-pass filtered (50-500 Hz) to reduce movement related artifacts and environmental noise, and full-wave rectified. EMG signal was then visually inspected. EMG data with remaining artifacts were excluded from subsequent analysis (mean percentage of discarded trails: 13.73%). For each participant and trial, the averaged EMG responses of *Corrugator Supercilii* and *Zygomaticus Major* muscles were subdivided in four time epochs (T1-T4) of 500 ms each, that were then normalized with respect to the baseline. Hence, an EMG normalized value above the 100% means an activation of a given muscle with respect to the baseline, whereas an EMG normalized value below the 100% indicates an inhibition of that muscle with respect to the baseline. Mean EMG responses were then calculated for each Modality (AVC, AVI, Audio, Video), Emotion (Laugh, Cry, Control) and Period (T1, T2, T3, T4). EMG data were entered into a 4

(Modality: AVC, AVI, Audio, Video) × 3 (Emotion: Laugh, Cry, Control) × 4 (Period: T1: 0-500 ms, T2: 500-1000 ms, T3: 1000-1500 ms, T4: 1500-2000 ms) repeated measures ANOVA, with Modality, Emotion and Period as the within-participants factors. One separated ANOVA was conducted for each muscle (Corrugator and Zygomaticus).

BSABS scores

BSABS items were grouped into seven *a priori* scales, following Parnas and colleagues' previous work (Parnas et al., 2003). The seven *a priori* scales aimed to capture essential dimensions of the schizophrenia spectrum pathology (Parnas & Handest, 2002; Parnas & Bovet, 1991; Parnas 1999; Parnas, 2000) and were the following:

1. *Diminished affectivity* (DA): comprises items exploring a general decline in the affective potential;

2. *Disturbed contact* (DC): investigates a subjectively experienced discomfort in the interpersonal and social contexts;

3. *Perplexity* (PY): describes a disturbed pre-reflective articulation or loss of immediate grip of meaning;

4. *Cognitive Disorder* (CD): made of items describing experience of alterations in the cognition processes;

5. *Self-disorder* (SD): explores anomalies of self-awareness;

6. *Cenesthesias* (CEN): examines anomalies of awareness of the body;

7. *Perceptual disorder* (PD): describes perceptual distortions.

The interview items were coded as 0 (not present) or 1 (present). First, we checked for a good internal consistency, by means of coefficient alpha (Cronbach, 1951) computation for each scale. In order to maximize coefficient alpha, each scale was subjected to an item analysis, and those which tended to degraded alpha coefficient significantly were removed from the original item pool.

Finally, only the scales that reached an α value ≥ 0.55 were taken into account for the subsequent correlation analyses.

For all performed analyses, P-values < 0.05 were considered to be statistically significant. Post-hoc comparisons (Fisher's test) were applied on all significant main effects and interactions.

3.3 Results

Behavioral results

Results of the analysis performed on behavioral rating scores showed that the factor Emotion was significant ($F_{2,34} = 60.31$ p < 0.000 $\eta^2_p = 0.78$). Post-hoc comparisons showed that Cry was rated by SzSp participants negatively than Laugh and Control stimuli were considered as neutral (all $p_s < 0.001$). Moreover, the interaction Modality × Emotion was also significant ($F_{2,34} = 51.81$ p < 0.000 $\eta^2_p = 0.75$) (see Fig. 1) meaning that during AVI modality, SzSp based their ratings following the visual content of the stimuli, that is, cry in AVI Laugh condition (in which participants saw crying and heard laughing) and laugh in AVI Cry (in which participants saw laughing and heard crying) (AVI Laugh vs. other modalities, all $p_s < 0.000$; AVI Cry vs. other modalities, all $p_s < 0.000$). Complementing these findings, post-hoc comparisons also demonstrated that Control stimuli were considered as devoid of any emotional content in all modalities (all $p_s > 0.05$).
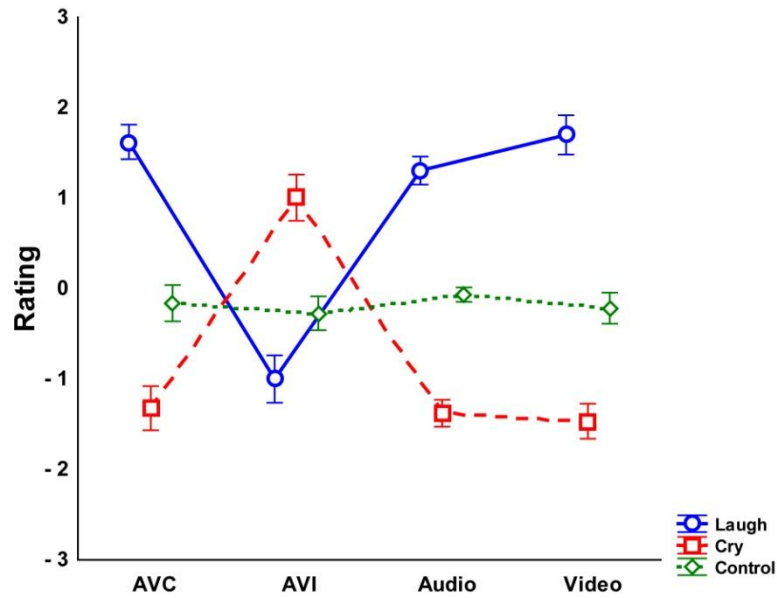
Figure 1. Averaged rating scores detected for each modality (AVC: Audio-Visual Congruent, AVI: Audio-Visual Incongruent; A: Audio, V: Video) and emotion (Laugh, Cry, Control). Error bars represent standard errors of mean (SE).

EMG results

In order to assess *Zygomatic Major* and *Corrugator Supercilii* EMG responses, two repeated measures ANOVAs were performed during the presentation of the stimuli of positive, negative and neutral facial expressions and/or related sounds in four different modalities (AVC, AVI, Audio, Video).

Zygomaticus Major muscle

The ANOVA carried out on *Zygomaticus Major* muscle EMG responses provided no significant main effects and interactions (all $p_s > 0.05$).

Corrugator Supercilii muscle

The analysis of *Corrugator Supercilii* muscle EMG responses revealed a significant main effect of Modality ($F_{3,51} = 3.10$ $p < 0.04$ $\eta^2_p = 0.15$), Emotion ($F_{2,34} = 6.50$ $p < 0.01$ $\eta^2_p = 0.28$) and

Epoch ($F_{3,51} = 8.78$ p < 0.001 $\eta^2_p = 0.34$) factors. Moreover, the interactions Modality × Emotion ($F_{6,102} = 2.68$ p < 0.05 $\eta^2_p = 0.14$), Modality × Epoch ($F_{9,153} = 2.32$ p < 0.05 $\eta^2_p = 0.12$) and Emotion × Epoch ($F_{6,102} = 2.66$ p < 0.05 $\eta^2_p = 0.19$) were all significant.

Of most interest, a significant interaction of all factors Modality × Emotion × Epoch was also detected ($F_{18,306} = 3.46$ p < 0.001 $\eta^2_p = 0.17$) (see Fig. 2). Since in behavioral rating analyses we observed that Control stimuli had been rated successfully rated as neutral by SzSp participants, we could accordingly proceed to contrast EMG activity recorded during Control stimuli with that detected during Laugh and Cry stimuli separately for each modality, as already done in the previous work where we employed the same paradigm (Sestito et al., 2013). Giving that the principal aim of this study is to identify only EMG activations, we therefore ignored EMG inhibitions, focusing our attention on emotions that in the previous study (Sestito et al., 2013) have been demonstrated to be effective in eliciting EMG Corrugator muscle responses in each modality (i.e., cry in AVC, Audio and Video, and laugh in AVI, where participants saw crying while heard laughing).

In AVC modality, post-hoc comparisons revealed that in SzSp participants Corrugator EMG responses significantly occurred only during 1000-1500 ms time epoch after stimulus onset (T3, p < 0.05).

In AVI modality, instead, no significant activations were found (all $p_s > 0.05$).

In Audio modality, particularly, Corrugator EMG responses occurred suddenly, even before 500 ms after stimulus onset, that is, in the time epoch spanning from 0 to 1000 ms (T1, T2 all $p_s < 0.01$).

In Video modality, finally, Corrugator EMG responses appeared later, in the time epoch spanning from 500 to 2000 ms after stimulus onset (T2, T3, T4; all $p_s < 0.01$).

To summarize, EMG activations in SzSp participants emerged only in Corrugator muscle, during the following conditions: AVC cry only in T3, Audio Cry in T1 and T2, and Video cry in T2, T3, T4; whereas no activations were found, finally, in AVI laugh condition.

Corrugator Supercilii
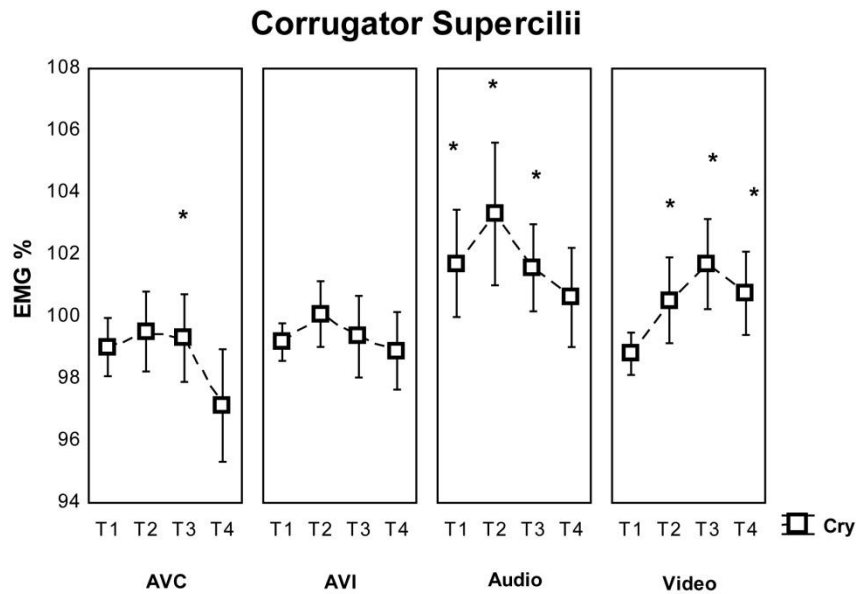
Figure S2. Mean EMG responses recorded for *Corrugator Supercilii* muscle for cry emotional stimuli in each modality [AVC (Audio-Visual Congruent), AVI (Audio-Visual Incongruent), Audio (Auditory) and Video (Visual)]. The significant activations with respect to Control stimuli are indicated by asterisks. Y-axis: 100% represents the mean EMG response of the baseline. X-axis: Time Epochs (T1: 0-500 ms, T2: 500-1000 ms, T3: 1000-1500 ms, T4: 1500-2000 ms). Error bars represent standard errors of mean (SE).

BSABS item analyses results

After item analyses, only five out of the original seven *a priori* scales survived, reaching an α coefficient $\geq$ 0.55: *Diminished affectivity* (DA), *Cognitive disorder* (CD), *Self-disorder* (SD), *Cenestesias* (CEN) and *Perceptual Disorder* (PD). These BSABS scales were then employed for the following correlation analyses with EMG activations showed by SzSp patients. For details about the scales and their item composition see Tab. 2.

Table 2. Parnas and colleagues (2003) *a priori* scales with Cronbach's αs and their BSABS item composition.

Diminished affectivity (DA; α = 0.55)
Diminished initiative and dynamism (A 4)
Anhedonia (A 6.1)
Diminished feelings for others (A 6.3)
Diminished need for interpersonal relations (A 6.4)

67

Cognitive disorder (CD; α = 0.59)

    Though blockages (C 1.4)

    Disorder of expressive language (C 1.7)

    Diminished thought initiative and goal-directedness of thinking (C 1.13)

Self Disorder (SD; α = 0.73)

    Psychic depersonalization (B 3.4)

    Somatic depersonalization (D 1.1)

    Other optic perception disturbances, including the "mirror phenomenon"

    (e.g., impression of a change in one's mirror image) (C 2.3)

Cenesthesias (CEN; α = 0.71)

    Electrical bodily sensations (D 5)

    Sensation of movement, pressure or pulling in the body or on the body surface (D 7)

    Sensation of lightness, heaviness, levitation, falling (D 8)

    Sensation of constriction, dilatation, shrinking or expansion of the body (D 9)

Perceptual Disorder (PD; α = 0.62)

    Unclear sight, transitory blindness, partial sight (C 2.1)

    Photopsia (C 2.2)

    Other optic perception disturbances (C 2.3)

    Changes of intensity or quality of acoustic perception (C 2.5)

Correlations between EMG activations and BSABS *a priori* scales

The specific aim of EMG analyses, in this study, was to detect EMG significant activations with respect to control condition, in different emotions (laugh and cry; that is, positive and negative emotions domain), modalities (AVC, AVI, Audio e Video) and time-epochs (T1: 0-500 ms; T2: 500-1000 ms; T3: 1000-1500 ms; T4: 1500-2000 ms).

EMG activations in SzSp participants emerged in Corrugator muscle for negative emotion during the following conditions: AVC cry only in T3 (i.e., the time epoch spanning from 1000 to 1500 ms after stimulus onset); in Audio Cry in T1 and T2 (i.e., from 0 to 1000 ms after stimulus onset); in Video cry in T2, T3, T4 (i.e., from 500 to 2000 ms after stimulus onset). No activations were found, finally, in AVI laugh.

Furthermore, the analysis performed on *Zygomaticus Major* muscle EMG responses to positive emotion on the other hand, yielded no significant results.

After item analyses, only five out of the original seven *a priori* scales survived (reaching an alpha coefficient ≥ 0.55, that was considered adequate): *Diminished affectivity* (DA), *Cognitive disorder* (CD), *Self-disorder* (SD), *Cenestesias* (CEN) and *Perceptual Disorder* (PD) (for item composition and αs coefficients, see Appendix A). Subsequently, Pearsons' correlations were calculated between SzSp participants' EMG activations and BSABS *a priori* scales previously selected via item analysis.

Strikingly, among all variables we tested, only EMG activations detected in Audio cry condition, both in T1 and T2, disclosed a robust positive correlation with *Self-Disorder* (SD) BSABS scale (T1, $r = 0.518$ $p < 0.03$; T2, $r = 0.506$ $p < 0.04$) (see Fig. 3).

Figure 3. Pearson's correlations between *Self-disorder* (SD) scale and EMG activations recorded during Audio Cry condition, in T1 (A) and T2 (B) time-epochs.

For all the other BSABS scales and EMG data, no significant correlations were found (all $p_s > 0.05$) (Table 3).

Table 3. Pearsons' correlations between EMG activations and subjective experience domains as measured by Parnas et colleagues *a priori* scales (Parnas et al., 2005). Asterisks mean a statistical significant level ($p < 0.05$).

EMG Corrugator activations	DA	CD	SD	CEN	PD
AVC Cry (T3)	0.185	- 0.260	0.262	- 0.015	- 0.192
AUDIO Cry (T1)	- 0.250	0.000	**0.518***	0.109	0.296
AUDIO Cry (T2)	- 0.198	- 0.057	**0.506***	0.074	0.135
VIDEO Cry (T2)	- 0.095	- 0.019	0.008	- 0.331	- 0.431
VIDEO Cry (T3)	0.196	0.028	0.066	- 0.049	- 0.136
VIDEO Cry (T4)	0.116	- 0.157	- 0.120	- 0.258	- 0.261

3.4 Discussion

First of all, our study clearly demonstrates an imbalance in emotional motor resonance in SzSp patients: indeed, no significant effects of emotion and modality were found for positive emotions, whereas, coherently with our previous study (Sestito et al., 2013) a significant facial emotional resonance occurred when participants perceived negative emotional stimuli. Noteworthy, strong and long-lasting EMG activations were found for "single-sensory" modalities (i.e., Audio and Video) whereas when multisensory modalities were involved, EMG activation only occurred with AVC modality in a single temporal epoch and no EMG activation was detected in AVI modality. Moreover, when participants perceived stimuli in Audio modality, EMG activations occurred rapidly (even in the time epoch between 0 and 500 ms after stimuli onset), while in Video modality EMG activations arose later.

The imbalance in emotional motor resonance showed by SzSp patients, with a selective bias toward negative stimuli, could be interpreted as evidence for the *aberrant assignment of salience* (Kapur, 2003) to negative stimuli. The prevalence of pessimistic, depressing stimuli and the complete absence of resonance to positive stimuli, could be directed to external everyday living as well as toward internal psychopathological thoughts, perceptions and feelings, which in turn, could amplify patients' receptiveness and sensitivity to their own psychotic symptoms (e.g., delusions and hallucinations).

Furthermore, consistently with previous findings, our study revealed a multisensory integration impairment consisting of a selective deficit involving multisensory modalities as AVC e

AVI and a simultaneous heightened sensitivity for "single-sensory" modalities (see Postmes et al., 2013 for a review). Of most interest, very recently, Postmes and colleagues (2013) hypothesized that an extreme imbalance between different types of sensory input could hinder their integration within a single unified percept, leading to the well documented multisensory audio-visual disintegration in schizophrenia. Interestingly, these authors directly related sensory disintegration to disintegration of the self. This happens because every single sensory modality, with its properties, contributes to inform the self about the environment *via bottom-up* processes, and conflicting sensory inputs results in sensory ambivalence, bringing forth contradictory experiences. As a consequence, on the one hand sensory amplification (i.e., an increased impact or salience) of any thought or sensory detail occurs, and on the other, a reduced attention for other meaningful events takes place, hence driving patients to a resultant disintegration of their experiential world. What happens in this case shows many analogies with what phenomenological psychiatrists call "*diminished presence*" (Sass & Parnas, 2003; Cermolacce et al., 2007; Gallagher, 2005), viewed as due to incoherence between the inner bodily patterns of sensory information (Damasio, 2001) and environmental occurrences, leading to deep changes of subjective experience (De Vries et al., 2013). This perceptual incoherence creates a misalignment between *mind* and *bodily self*, inducing disturbances of subjective experience as depersonalization, blurred boundaries, cenesthopathies or diminished sense of ownership and agency. Thus, any deficits in somatosensory feedback, as a lack of facial motor resonance in response to emotional positive stimuli, plus an imbalance of "single-sensory" modalities favoring the negative ones as we found in our study, could function as a "sensory vacuum", that may undermine the perceived bodily self (Ferri et al., 2012; Gallese & Ferri, 2013; Ferri et al., 2013). Notably, self-disorders expressions are often present long before the first psychotic episode and could hence be predictive for psychosis onset (Nelson et al., 2012).

Most interestingly, in our study we found a robust correlation between self-disorders scale and both EMG corrugator facial activations in response to negative stimuli, presented only in

auditory modality. These findings strikingly point to a fundamental role of auditory modality salience for negative stimuli in schizophrenia (Parnas & Handest, 2003).

In sum, imbalance in somatosensory feedback toward negative stimuli and single-sensory modalities lead to perceptual incoherence and hence to disjointed self-experiences, described as "self-disorders" by phenomenological psychiatrists, regarded as the core deficit in schizophrenia. Moreover, EMG activations in response to auditory negative stimuli strongly correlate with self-disorders, meaning that the *aberrant salience* (Kapur, 2003) of auditory negative stimuli perhaps plays a key role in schizophrenia pathology (e.g., in auditory hallucinations). The paradigm employed in this study could provide a useful framework to better understand perceptual incoherence, thus allowing to track disease susceptibility of high-risk individuals and improving recognition of early stages of schizophrenia. Indeed, schizophrenia is often preceded by sub-delusional detachment from reality that can be regarded as manifestation of self-disorders (Schultze-Lutter, 2010; Nelson et al., 2012; Parnas et al., 2011) or perceptual incoherence. This paradigm, allowing the exploration of the bodily motor resonance in response to different perceptual modalities and emotional valence, might be a promising heuristic model to investigate multisensory disintegration and perceptual incoherence as possible early markers of schizophrenia, given their close connection with self-disorders, particularly in clinical asymptomatic, genetically high-risk individuals.

References

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th edn.* Washington: The American Psychiatric Association.

Andreasen, N. C. (1984a). *Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City: University of Iowa.

Andreasen, N. C. (1984b). *Scale for the Assessment of Negative Symptoms (SANS).* Iowa City: University of Iowa.

Andreasen, N. C., Pressler, M., Nopoulos, P., Miller, D., and Ho, B.-C. (2010). Antipsychotic Dose Equivalents and Dose-Years: A Standardized Method for Comparing Exposure to Different Drugs. *Biol Psychiatry*. 67, 255–262.

Arbib, M.A., and Mundhenk, T.N. (2005). Schizophrenia and the mirror system: an essay. *Neuropsychologia.* 43, 268-280.

Bar, K. J., Berger, S., Metzner, M., Boettger, M. K., Schulz, S., Ramachandraiah, C. T., Terhaar, J., Voss, A., Yeragani, V. K., and Sauer, H. (2010). Autonomic dysfunction in unaffected first-degree relatives of patients suffering from schizophrenia. *Schizophr Bull*. 36, 1050–1058.

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., and Lenzi, G.L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A*. 100, 5497–5502 .

Catts, S.V., Fox, A.M., Ward, P.B., and McConaghy, N. (2000). Schizotypy: henotypic marker as risk factor. *Aust N Z J Psychiatry.* 34, s101–s107.

Chapman, L.J., and Chapman, J.P. (1987). The search for symptoms predictive of schizophrenia. *Schizophr Bull.* 13, 497–503.

Cermolacce, M., Naudin, J., and Parnas, J. (2007). The "minimal self" in psychopathology: re-examining the self-disorders in the schizophrenia spectrum. *Conscious. Cogn.* 16, 703-714.

Corcoran, C., Davidson, L., Sills-Shahar, R., Nickou, C., Malaspina, D., Miller, T., and McGlashan, T. (2003). A qualitative research study of the evolution of symptoms in individuals identified as prodromal to psychosis. *Psychiatr Q*. 74, 313–332.

Cronbach, L.J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrica.* 16, 297-334.

Damasio, A. (2001). Fundamental feelings. *Nature*. 413, 781.

De Vries, R., Heering, H.D., Postmes, L., Goedhart, S., Sno, H.N., and de Hann. L. (2013). Self-disturbance in schizophrenia: a phenomenological approach to better understand our patients. *The primary care companion to CNS disorders.* 15, PCC.12m01382.

Decety, J., and Chaminade, T. (2003). When the self represents the other: A new cognitive neuroscience view on psychological identification. *Consciousness and Cognition*. 12, 577–596.

Derntl, B., Finkelmeyer, A., Toygar, T. K., Hülsmann, A., Schneider, F., Falkenberg D. I., and Habel, U. (2009). Generalized deficit in all core components of empathy in schizophrenia. *Schizophr Res.* 108, 197-206.

Ferri, F., Costantini, M., Salone, A., Di Iorio, G., Martinotti, G., Chiarelli, A., Merla, A., Di Giannantonio, M., and Gallese, V. (2013). Upcoming tactile events and body ownership in schizophrenia, *Schizophr. Res.* http://dx.doi.org/10.1016/j.schres.2013.06.026.

Ferri, F., Frassinetti, F., Mastrangelo, F., Salone, A., Ferro, F.M., and Gallese V. (2012). Bodily self and schizophrenia: the loss of implicit self-body knowledge. *Conscious. Cogn.* 21, 1365-1374.

Fuchs, T. (2005). Corporealized and Disembodied Minds: A Phenomenological View of the Body in Melancholia and Schizophrenia. *Philos Psychiat Psychol.* 12, 95-107.

Gallagher, S. (2005). *How the body shapes the mind.* Cambridge: University Press.

Gallese, V. (2001). The 'shared manifold' hypothesis: From mirror neurons to empathy. *J Consc Stud.* 8, 33-50.

Gallese, V. (2003). The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology* 36, 171-180.

Gallese, V. (2005). Embodied simulation: From neurons to phenomenal experience. *Phenomenol Cogn Sci.* 4, 23-48.

Gallese, V., and Ferri, F. (2013). Jaspers, the body and Schizophrenia. The bodily self. *Psychopathology.* 46, 330-336.

Gross, G., Huber, G., Klosterkoetter, J., and Linz, M. (1987). *BSABS: Bonner Skala fur die Beurteilung von Basissymptomen.* Berlin, Germany: Springer; 1987. Italian translation by Maggini C, Dalle Luche R, eds. Pisa (Italy): ETS; 1992.

Handest, P., and Parnas, J. (2005). Clinical characteristics of first-admitted patients with ICD-10 schizotypal disorder. *Br J Psychiatry.* 48, s49–s54.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psych.* 160, 13-23.

Klosterkotter, J., Hellmich, M., Steinmeyer, E.M., and Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry.* 58, 158–164.

Maggini, C., and Raballo, A. (2003). Subjective experience of personality dimensions in 1st degree relatives of schizophrenics. *Acta Biomed.* 74, 131–136.

Maggini, C., and Raballo, A. (2004). Subjective experience of schizotropic vulnerability in siblings of schizophrenics. *Psychopathology.* 37, 23–28.

Mass, R. (2000). Characteristic subjective experiences of schizophrenia. *Schizophr Bull.* 26, 921–931.

Møller, P., and Husby, R. (2000). The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. *Schizophr Bull.* 26, 217–232.

Nelson, B., Thompson, A., and Yung, A.R. (2012). Basic self-disturbance predicts psychosis onset in ultra high risk for psychosis "prodromal" population. *Sch Bull.* 38, 1277-1287.

Niedenthal, P. M. (2007). Embodying emotion. *Science.* 316, 1002–1005.

Niedenthal, P. M., Winkielman, P., Mondillon, L., and Vermeulen, N. (2009). Embodiment of emotion concepts. *J Pers Soc Psychol.* 96, 1120-1136.

Parnas, J. (1999). From predisposition to psychosis: progression of symptoms in schizophrenia. *Acta Psychiatr Scand.* 99, 20-29.

Parnas, J. (2000). The self and intentionality in the pre-psychotic stages of schizophrenia: A phenomenological study. In D. Zahavi (Ed.), *Exploring the self: Philosophical and psychopathological perspectives on self-experience* (pp. 115-148). Amsterdam, Netherland: John Benjamins.

Parnas, J., and Bovet, P. (1991). Autism in schizophrenia revisited. *Compr Psychiatry.* 32, 7-21.

Parnas, J., and Handest, P. (2003). Phenomenology of anomalous self-experience in early schizophrenia. *Compr Psychiatry.* 44, 121-134.

Parnas, J., Handest, P., Jansson, L., and Saebye, D. (2005). Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology.* 38, 259–267.

Parnas, J., Handest, P., Sæbye, D., and Jansson, L. (2003). Anomalies of subjective experience in schizophrenia and psychotic bipolar illness. *Acta Psychiatr Scand.* 108, 126–133.

Parnas, J., Jansson, L., Sass, L.A., and Handest, P. (1998). Self-experience in the prodromal phases of schizophrenia. *Neurol Psychiatry Brain Res.* 6, 97–106.

Parnas, J., Møller, P., Kircher, T., Thalbitzer, J., Jansson, L., Handest, P., and Zahavi, D. (2005). EASE: Examination of Anomalous Self-experience. *Psychopathology.* 38, 236–258.

Parnas, J., Raballo, A., Handest, P., Jansson, L., Vollmer-Larsen, A., and Sæbye, D, (2011). Self-experience in the early phases of schizophrenia: 5-year follow-up of the Copenhagen Prodromal Study. *World Psychiatry.* 10, 200-204.

Postmes, L., Sno, H.N., Goedhart, S., van der Stel, J., Heering, H.D., and de Haan, L. (2013). Schizophrenia as a self-disorder due to perceptual incoherence. *Sch Res.* http://dx.doi.org/10.1016/j.schres.2013.07.027.

Raballo, A., and Parnas, J. (2011). The silent side of the spectrum: Schizotypy and Schizotaxic Self. *Schizophr Bull.* 7, 1017-1026

Raballo, A., Saebye, D., and Parnas, J. (2011). Looking at the schizophrenia spectrum through the prism of self-disorders: an empirical study. *Schizophr Bull.* 37, 344–351.

Sass, L.A., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr Bull*. 29, 427-444.

Schultze-Lutter, F. (2009). Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophr Bull*. 35, 5–8.

Schultze-Lutter, F., Klosterkoetter, J., Picker, H., Steinmeyer, E.M., and Ruhrmann, S. (2007a). Predicting first-episode psychosis by basic symptom criteria. *Clin Neuropsychiatry.* 4, 11–22.

Schultze-Lutter, F., Ruhrmann, S., Berning, J., Maier, W., and Klosterkotter, J. (2010). Basic symptoms and ultrahigh risk criteria: symptom development in the initial prodromal state. *Schizophr Bull.* 36, 182–191.

Schultze-Lutter, F., Ruhrmann, S., Hoyer, C., Klosterkoetter, J., and Leweke, F.M. (2007b). The initial prodrome of schizophrenia: different duration, different underlying deficits? *Compr Psychiatry.* 48, 479–488.

Schultze-Lutter, F., Ruhrmann, S., Picker, H., von Reventlow, H.G., Brockhaus-Dumke, A., and Klosterkoetter, J. (2007c). Basic symptoms in early psychotic and depressive disorders. *Br J Psychiatry.* 51, s31–s37.

Sestito, M., Umiltà, M.A., De Paola, G., Fortunati, R., Raballo, A., Leuci, E., Maffei, S., Tonna, M., Amore, M., Maggini, C. and Gallese, V. (2013). Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front Human Neurosci.* doi: 10.3389/fnhum.2013.00368.

Sonnby-Borgström, M. (2002). Automatic mimicry reactions as related to differences in emotional empathy. *Scand J Psychol.* 43, 433– 443.

Sonnby-Borgström, M., Jönsson, P., and Svensson, O. (2003). Emotional empathy as related to mimicry reactions at different levels of information processing. *J Nonverbal Behav.* 27, 3–23.

Varcin, K. J., Bailey, P. E., and Henry, J. D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. *J Int Neuropsychol Soc.* 16, 621-629.

Wieneke, A., Schultze-Lutter, F., Steinmeyer, E.M., and Klosterkotter J. (1997). Abnormal subjective experiences and neuropsychological deficits in first-degree relatives of schizophrenics. *Schizophr Res.* 24, 49.

Chapter 4

4. Anomalous Echo: Exploring abnormal experience correlates of emotional motor resonance in Schizophrenia Spectrum patients.

4.1 Introduction

In recent years, the issues of subjective experiences occurring in Schizophrenia have once again become central topics in psychopathological research. Among self-experiential disturbances, basic symptoms (BS), stemming from Jasperian phenomenological psychopathology, are considered the first subjective reverberation of the entailed neurobiological underpinnings of schizophrenia. Anomalous subjective experiences have been demonstrated to occur in different schizophrenia-related conditions (i.e., full-blown schizophrenia, prodromal conditions, schizotipy, and among genetically high-risk individuals) (Møller & Husby, 2000; Klosterkötter et al., 2001; Parnas et al., 1998; Parnas et al., 2005; Schultze-Lutter et al., 2007a; Schultze-Lutter et al., 2007b; Schultze-Lutter et al., 2007c; Parnas et al., 2003; Mass, 2000; Chapman & Chapman, 1987; Catts et al., 2000; Parnas, 2000; Handest & Parnas, 2005; Raballo et al., 2011; Wieneke et al., 1997; Maggini & Raballo, 2004; Raballo & Parnas, 2011) thus fostering research on the underlying psychobiological processes by means of a prominent emphasis on schizophrenia experiential and behavioral manifestations. Over recent years, some researchers have argued that insights from phenomenological psychiatry may be usefully applied to early intervention efforts, in the areas of early identification (Nelson et al., 2008; Parnas, 2005), prediction of outcome (Nelson et al., 2008), and therapeutic work (Nelson et al., 2009).

BS are subtle phenomena privately experienced by the patients, clinically devoid of accompanying observable signs, as they belong to the subjective experience domain. BS have been conceived (Huber, 1983) as the first phenomenological correlate of disturbances that underlie psychopathological manifestations of the disorder. Thus, BS are likely to identify subtle expressions of genetic liability to schizophrenia, subjectively perceived as unelaborated, yet discomforting, interferences in daily experience (Huber, 1983; 1992; Gross, 1989). Phenomenology oriented

researchers have proposed that principally, a disturbance of the basic sense of the self is a phenotypic trait marker of psychotic vulnerability to Schizophrenia Spectrum (SzSp) disorders (Nelson et al., 2008; Parnas, 2000; 2003; Parnas et al., 2005; Parnas et al., 1998; Sass & Parnas, 2003). Disturbances of basic self-experience evident in SzSp conditions include disturbed sense of presence, corporeality, stream of consciousness, self-demarcation and existential reorientation, all of which are intimately interrelated (Parnas 2003; Parnas & Sass, 2001).

Recent works (Nelson et al., 2013a; 2013b), outlined how various aspects of the phenomenological basic self-disturbances occurring in schizophrenia might correlate with neurocognitive disturbances, suggesting avenues for empirical enquiry into these proposed associations. Noteworthy, a recent study of our research group (see Chapter 3, Sestito et al., in preparation), investigated a possible connection between phenomenological experience (i.e., the *mind* level) and physiological mechanisms (i.e., the *body* level) in SzSp patients, explored through the motor facial mimicry in response to emotional stimuli, previously demonstrated to be a consistent Mirror Neurons mechanisms *proxy* (Derntl et al., 2012; Carr et al., 2003; Gazzola et al., 2006; Molnar-Szakacs et al., 2006; Seitz et al., 2008; Molnar-Szakacs and Uddin, 2013). We found an imbalance in emotional motor resonance with a selective bias toward negative stimuli in patients, as well as a multisensory integration impairment. Of most interest, we discovered a robust correlation between Self-disorders scale and Electromyographic facial reactions in response to negative stimuli, presented only in auditory modality. The result of our study encourage research into disturbed mirror neurons mechanism as possible brain-level correlates of disturbed subjective experiences in SzSp, providing a key unifying or integrative construct to address future trans-domain research in the neurobiology of vulnerability to schizophrenia. Besides a sensitivity for negative stimuli, in a previous study (Sestito et al., 2013) schizophrenia patients showed, with respect to healthy controls, a "non-specific" Zygomaticus muscle response when positive (laugh) stimuli were presented (i.e., an inadequate "smile" response occurring both when laugh as well as cry stimuli were presented, thus defined by us as "non-specific" response). This phenomena has

some affinities with Heiman and Spoerri's *mimic disintegration* (1957) concept, that is, an indecipherable and bizarre mimic pattern, possibly due to a disruption of patients' ability to resonate with others' emotions through facial mimicry (i.e., embodied simulation mechanism disruption), that in turn, could contribute to the well known empathy deficits in schizophrenia (Derntl et al., 2012; Varcin et al., 2010). Recent findings, demonstrated that involuntary facial mimicry to emotional stimuli constitutes an important low-level mechanism that leads to feel what others feel, hence allowing a direct empathic understanding of others' emotions *via* their bodily simulation (Gallese, 2003; 2005; 2006; Niedenthal, 2007; Preston and De Waal, 2002; Sonnby-Borgström, 2002). Further studies investigating findings integration across the phenomenological and neurocognitive "levels" are hence necessary, in order to provide significant advances in the understanding of vulnerability markers in schizophrenia and possibly enhance early identification and intervention strategies.

The aim of this study is to explore whether a weak or high emotional motor resonance occurring in SzSp is related to patients' clinical features and to their anomalous subjective experiences as indexed by the BSABS scale. In order to do this, we employed a novel paradigm proved to be sensitive in evoking a congruent facial mimicry (measured by means of physiological facial Electromyographic activity, EMG) through multimodal stimuli. This paradigm has proven to detect deficits in facial mimicry in schizophrenia patients (Sestito et al., 2013).

In order to explore what subjective anomalous experiences characterize SzSp patients with a different degree of motor resonance to emotional stimuli, participants will be divided into two groups (i.e., Internalizers and Externalizers) based on their low (i.e., Internalizers) and high (i.e., Externalizers) emotional resonance, following the same method used in previous work (Sestito et al., 2013). Clinical features (positive and negative symptoms, length of illness, age at first psychosis and number of psychotic episodes) and anomalous subjective experiences (BSABS scores) differences between these two cohorts were then explored.

82

4.2 Methods

Sample

The sample, recruited at the Psychiatry Section of Parma University Department of Neuroscience, included nineteen outpatients (fourteen males, five females, mean age 34.1 years SD ±6.73) diagnosed with a Schizophrenia Spectrum disorder (i.e. schizophrenia or schizotypal personality disorder according to DSM-IV diagnostic criteria (1994)). All of them were clinically stable (i.e., with no current psychotic symptoms) at the time of the assessment.

General psychopathology was assessed with the Scales for the Assessment of Positive and Negative Symptoms (Andreasen, 1984a; 1984b).

All patients were screened to rule out any history of neurological and vascular disorders, alcohol or drugs abuse and mental retardation. Patients were receiving different antipsychotic medications, and to quantify them we obtained the cumulative measure of lifetime drugs exposure following the method adopted by Andreasen and colleagues (2010). Demographic and psychopathological features of the sample are provided in Table 1.

Table 1. Demographic variables and psychopathological characteristics of Schizophrenia Spectrum (SzSp) sample. Drugs are expressed as the cumulative value measured in dose-years in the form of (chlorpromazine equivalent in mg) × (time on dose measured in years) (Andreasen et al., 2010).

Characteristic	Mean	DS	Range
Age (years)	34.11	6.73	25-49
SAPS	24.01	16.26	0-170
SANS	46.34	17.63	0-125
BSABS	41.72	16.52	0-103
Lenght of illness (years)	11.06	4.84	2-24
Age at first psychosis	24.06	4.30	19-34
Number of psychotic episodes	3.35	1.82	0-7
Dose of typical and atypical antipsychotics	26.41	19.54	
Dose of atypical antipsychotics	20.01	15.64	
Dose of typical antipsychotics	6.40	5.72	

Written informed consent was obtained from all participants before entering the study, after the treating clinician gave them an exhaustive explanation about how the study would be conducted. The Ethics Committee of the University of Parma approved the study, that was carried out according with the ethical standards of the Declaration of Helsinki.

BSABS interview

Disturbances of subjective experience were investigated through the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Gross et al., 1992). The BSABS is a 98-item semi-structured interview measuring subjective uncharacteristic experiences with a disturbing quality (i.e. BS). These symptoms have been empirically clustered into five subsyndromes (Klosterkötter et al., 1996; Klosterkötter et al., 1997; Bechdolf et al., 2002):

1. *Thought, language, perception and motor disturbances* (formerly termed "information processing disturbances") cluster includes BS involving autopsychic dissonance in cognition, naturalness of agency, perception and linguistic interaction.

2. *Impaired bodily sensations* (termed "coenesthesias"), includes a cluster of cenesthesic BS, mainly affecting bodily proprioceptive reflexive and prereflexive sensory awareness.

3. *Impaired tolerance to normal stress* cluster (termed "vulnerability"), includes some BS characterized by abnormal intolerance to social, working and attentional demands stemming from the daily environmental engagement.

4. *Disorders of emotion and affect* cluster (termed "adynamia") includes so-called "adynamic" BS, associated with a lack of dynamic-affective empowerment of emotional and attentional goal directedness.

5. *Increased emotional reactivity* cluster (formerly named *"interpersonal irritation"*) is defined by BS expressing hyperreactivity, enhanced impressionability and disturbances in emotional responsiveness.

Experimental paradigm: stimuli and procedure

The experimental paradigm, validated and detailed in a previous study (see Chapter 2, Sestito et al., 2013), consists of the following procedure. Participants were presented with stimuli portraying positive (laugh), negative (cry) and neutral (control) emotional stimuli in visual (i.e., Video), auditory (i.e., Audio) modalities in isolation, and congruently (i.e., Audio-Visual Congruent, AVC) or incongruently (i.e., Audio-Visual Incongruent, AVI) associated. Participants were requested to recognize and quantitatively rate how much positive or negative the positive or negative the perceived stimulus was, while EMG activity of *Corrugator Supercilii* and *Zygomaticus Major* muscles was recorded. For further details about stimuli, experimental procedure and EMG recording, please refer to Sestito and colleagues' (2013).

Data analysis

Internalizers and Externalizers

In order to divide into two groups SzSp patients based on their low/high motor resonance, we followed the same method used in previous work (Sestito et al., 2013). First, we considered the whole participants' group and we calculated its median EMG response, separately for each emotion valence (positive, negative), irrespective of modalities and periods. Then, specifically for each participant, we calculated his/her median EMG response for each emotion valence (positive, negative). If participant's EMG value was equal or greater than the median value previously calculated for the whole group, we classified this participant as Externalizer (i.e., with higher EMG response with respect to the median group's value). If, on the other hand, this value was smaller than the median value previously calculated for the whole group, we classified this participant as Internalizer (i.e., with lower EMG response with respect to the median group's value).

Following this procedure, for positive emotions we obtained the median EMG value of 94.36% (10 Externalizers and 9 Internalizers) whereas for negative emotions, we calculated a median EMG value of 100,00% (10 Externalizers and 9 Internalizers).

BSABS item analyses

BSABS items were grouped into five clusters covering five main phenomenological areas (1. *Information processing disturbances*, 2. *Coenesthesias*, 3. *Vulnerability*, 4. *Adynamia*, 5. *Interpersonal Irritation*). The interview items were coded as 0 (not present) or 1 (present).

First, we checked for a good internal consistency, by means of coefficient alpha (Cronbach, 1951) computation for each scale. In order to maximize coefficient alpha, each scale was subjected to an item analysis, and those which tended to degraded alpha coefficient significantly were removed from the original item pool. Finally, only the scales that reached a sufficient α value ($\geq$ 0.50) were taken into account for the subsequent analyses.

Internalizer/Externalizer cohorts' differences for clinical features and abnormal subjective experiences

In order to explore possible differences between SzSp Internalizer and Externalizer cohorts with respect to clinical features and abnormal subjective experiences, we ran a series of Mann-Whitney *U*-tests for independent groups. Separately for positive and negative emotion valence, we set EMG (Internalizers and Externalizers) as independent variable, and SAPS scores, SANS scores, BSABS scores (total; Clusters 1, 2, 3, 4, 5), length of illness, age at first psychosis and number of psychotic episodes, as dependent variables. Since some clinical information were incomplete for 2 patients and BSABS scores were not available for 1 patient, when data were missing, we excluded the specific case from analysis. For all performed analyses, the significance level was set at $p < .05$.

4.3 Results

BSABS scales item analyses

After item analyses, all BSABS clusters reached a sufficient alpha coefficient ($\geq$ 0.50; for item composition and αs coefficient for each cluster, see Table 2). Subsequently, Mann-Whitney *U*–

tests were run using all BSABS clusters previously adjusted via item analysis to obtain a good internal consistency.

Table 2. BSABS Clusters with Cronbach's αs and item composition.

Cluster 1 – Thought, language, perception and motor disturbances
(Information processing disturbances, α = 0.72)
A6-2, C1-1, C1-2, C1-3, C1-4, C1-6, C1-7, C1-10, C1-15, C1-16, C1-17, C2-1, C2-2, C2-3, C2-4, C2-5, C2-6, C2-8, C2-9, C3-1, C3-2, C3-3.
Cluster 2 – Impaired bodily sensations (Coenesthesias, α = 0.88)
D1, D1-1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, D14.
Cluster 3 – Impaired tolerance to normal stress (Vulnerability, α = 0.54)
A8-4, B1-3+A8-2, B1-4+A8-3, B1-2+A8-1, B1-1.
Cluster 4 – Disorders of Emotion and Affect (Adynamia, α = 0.57)
C1-5, C1-8, C1-9, C1-12, C1-13, A6-1, A6-4.
Cluster 5 – Increased emotional reactivity (Interpersonal Irritation, α = 0.52)
B2-1, B2-2, B2-3, A7-2.

Internalizer/Externalizer cohorts' differences for clinical features and abnormal subjective experiences

For positive emotions, we found that Externalizer SzSp patients presented higher scores in BSABS Cluster 5 (Interpersonal Irritation, for item composition see Table 3) with respect to Internalizers ($n = 18$; U = 16.5 $p < 0.04$) (Fig. 1, upper panel).

For negative emotions, we found that Externalizer SzSp patients had more psychotic episodes ($n = 17$; U = 14 $p < 0.05$) as well as higher scores in BSABS Cluster 3 (Vulnerability, for item

composition see Table 3) with respect to Internalizers ($n = 18$; U = 14 p < 0.02) (Fig. 1, lower panel).

For all the other clinical features, we found no significant results (all $p_s > 0.05$).

Table 3. BSABS Cluster 3 and Cluster 5 item composition.

Cluster 3: Impaired tolerance to normal stress (Vulnerability)	
A8-4	Inability to divide attention
B1-3 + A8-2	Impaired tolerance to certain social situations of everyday life that are primarily emotionally neutral
B1-4 + A8-3	Impaired tolerance to working under pressure or time or rapidly changing of different demands
B1-2 + A8-1	Impaired tolerance to unusual, unexpected or specific novel demands
B1-1	Impaired tolerance to everyday stress or routine work

| **Cluster 5: Increased emotional reactivity (Interpersonal Irritation)**	
B2-1	Increased emotional reactivity in response to everyday events
B2-2	Increased emotional reactivity in response to routine social interactions
B2-3	Increased emotional reactivity in response to misfortune to strangers
A7-2	Disturbances of emotional responsiveness as characterized by a decrease in facial expression, intonation and communication gestures
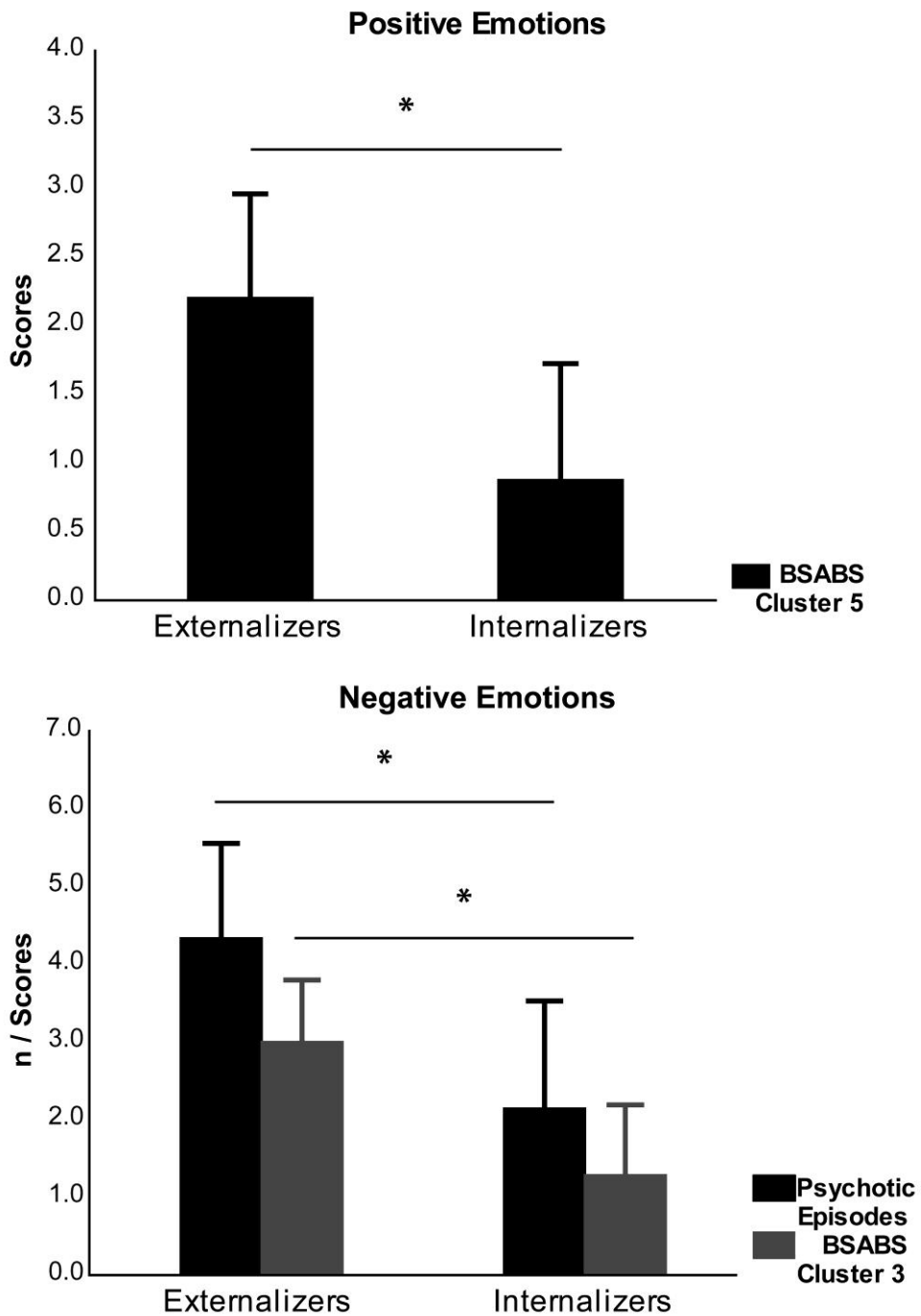
Figure 1. In the upper panel are showed BSABS Cluster 5 scores for Externalizer and Internalizer cohorts for positive emotions. In the lower panel are presented the number of psychotic episodes and BSABS Cluster 3 scores for Externalizer and Internalizer cohorts for negative emotions. All other conventions as in Figure 1.

4.4 Discussion

In this study we explored, by subdividing SzSp participants in two cohorts according to the intensity of their EMG congruent responses, whether a low (i.e., Internalizer participants) or high (i.e., Externalizer participants) emotional motor resonance to positive and negative stimuli is accompanied by specific anomalous subjective experiences as well as by given clinical characteristics.

Our study clearly demonstrates that SzSp patients more resonating with negative emotional stimuli (i.e., Externalizers for negative emotions), had significantly more psychotic episodes as well as higher scores in BSABS Cluster 3 (Vulnerability) than patients belonging to the Internalizers cohort. On the other hand, SzSp patients more resonating with positive emotional stimuli (i.e., Externalizers for positive emotions), showed higher scores in BSABS Cluster 5 (Interpersonal Irritation) than patients belonging to the Internalizers cohort.

These results cohere with previous findings, documenting the correlation between schizophrenia spectrum conditions (self-disorders particularly) and emotional motor resonance in response to negative stimuli (see Chapter 3, Sestito et al., in preparation) as well as an anomalous reaction of schizophrenia patients (i.e., an inadequate, "non-specific" response) toward positive stimuli (Sestito et al., 2013). We will use a phenomenological approach in order to shed new light upon the apparently unintelligible, puzzling, experiences of patients with schizophrenia in terms of a disruption of the normal self-perception. Our aim is to integrate the phenomenic, experiential, descriptive perspective with the physiological description of motor facial mimicry, hence allowing a unified view.

First, we found that patients more reacting to negative emotional stimuli (i.e., Externalizers), also had higher vulnerability BSABS cluster 3 scores and experienced more psychotic episodes. Vulnerability BSABS cluster comprises items describing patients' impaired tolerance to normal everyday stress, to unusual, unexpected or specific novel demands, to certain social situations of everyday life that are primarily emotionally neutral, to working under time pressure or with rapidly

changing demands (see Table 3). Recently, Nelson et al. (2013b) proposed an interesting integrative view that provides a coherent interpretation for our findings. A considerable amount of studies (for a review, see Nelson et al. 2013b) indicates that the failed suppression of attention to irrelevant stimuli and a concurrent excessive attention to the irrelevant ones, leads patients to experience an *aberrant salience* of objects and associations (Kapur, 2003). In this context, "salience" refers to the motivational properties of an irrelevant stimulus, which can cause it to attract attention and drive behavior inappropriately. In schizophrenia, neutrality of the background environment gets lost and claims attentional importance, hence disrupting the appropriate salience of everyday events and objects. In other words, using an expression taken from perception research, the normal figure-ground relationship gets disrupted. A selective bias (i.e., aberrant salience) toward negative stimuli with respect to the positive ones was also found in our previous studies (see Chapters 2 and 3, Sestito et al., 2013; Sestito et al., in preparation).

Aberrant salience of irrelevant stimuli makes the background or the "implicit" noteworthy, a process well described by phenomenological psychopathology with the concept of hyper-reflexivity (Nelson et al., 2013a), that is, an excessive attention being paid to aspects of experience that are normally tacit and remain in the "background" of awareness. This aberrant salience is thought to generate a distorted model of the environment founded on erroneous inference, thought to driving to the emergence of psychotic symptoms. BSABS cluster 3 also describes how irrelevant, meaningless stimuli could be endowed with potential significance, consistent with their increased arbitrary, internally generated aberrant interpretations. According to BSABS cluster 3 description, an excessive attention to irrelevant (i.e., *primarily neutral*) cues, results in learning inaccurate and irrelevant causal associations, that may be the basis of positive symptoms in schizophrenia. In a previous work, importantly, the tendency to ascribe meaning where none is present has been found to be a strong predictor of psychotic disorder onset in an at-risk population (Hoffman et al., 2007).

Moreover, in the present study, the stronger emotional motor resonance showed by Externalizer patients to negative stimuli is accompanied by higher patients' psychotic relapses and hence, by a greater psychopathological vulnerability. An imbalance in sensory stimuli perception (for a review, see Postmes et al., 2013) might arise from a failure in data-driven bottom-up (e.g., facial or bodily feedback) and predominantly concept-driven top-down (e.g., delusional thinking) loop processes. Low-level, body-related disturbances may have a crucial bottom-up influence on cognitive processes of "meaning-making" in schizophrenia. The disruption in the automatic, low-level ability to appropriately "integrate" sensory inputs or information with stored material, can disrupt the sense of continuity and consistency in the sense of the self, as well as compromise the individual's attunement to others and to the world (Stanghellini, 2004), contributing to a gradually developing instability of personal identity.

The second finding emerging from this study, was that patients more reacting to positive emotional stimuli (i.e., Externalizers for positive emotions), had also higher Interpersonal Irritation BSABS cluster 5 scores than patients belonging to the Internalizers cohort. In particular, Interpersonal Irritation BSABS cluster comprises items describing patients' increased emotional reactivity toward everyday events, routine social interactions, misfortune to strangers and finally, disturbances of emotional responsiveness as characterized by a decrease in facial expression, intonation and communication gestures. In our previous study (see Chapter 2, Sestito et al., 2013), we found that patients with schizophrenia showed an anomalous, "non-specific" EMG zygomaticus response both when positive (laugh) and negative (cry) stimuli were presented. We explained this strange response as a kind of *mimic disintegration* (Heimann & Spoerri, 1957). However, the novel evidence that this aberrant physiologic response correlates with a particular set of anomalous subjective experiences, could now help us to shed new light on this strange response. Of particular interest are the prototypical descriptions belonging to the item A.7.2 (included in the BSABS cluster 5) clearly explained in the BSABS scale Italian manual (see also EASE scale, item 1.16, Parnas et al., 2005):

"*Disturbances of emotional responsiveness (Selbstverfügbarkeit) as characterized by a decrease in facial expression, intonation and communication gestures*" (Gross et al., 1992).

"[The patient experiences a] *discordance between intended expression and the expressed*, [a] *subjective experience of not being able to express oneself according to one's feelings and emotions. The patient experiences that his speech, behavior, gestures and facial expressions are not in line, or congruent, with what he feels; his expressivity is felt to be disfigured and distorted and somehow beyond self-control.*" (Parnas et al., 2005).

Some prototypical descriptions are the following:

"*During social interactions (…), I feel a tense expression on my face as I ought to laugh or make a face, stupidly.*"

"*I laugh in such a beastly and ridiculous way, and I feel as I'm totally defaced. My face lineaments are completely altered. I have a different appearance now, my smile, my eyes, all is changed.*" (from BSABS Manual, Gross et al. 1992; our translation).

Interestingly, in the present study patients more resonating with positive stimuli, also experience these strange face change feelings, as if the aberrant "smile" reaction they show were something completely extraneous from what they feel. These descriptions are entirely consistent with what we found in our first study (see Chapter 2, Sestito et al., 2013), where "smile" EMG reaction occurred not only when patients perceived laughter, but also, oddly, when cry stimuli were showed. In this context, it is tempting to consider that a disrupted automatic facial mimicry could probably foster patients' sense of detachment and increasing disconnection between the "expressed" and the "felt" I, resulting in gradual scission of the self. Phenomenologically speaking, a sense of distance and even alienation from patient's own experience is defined as "*disturbed presence*" (Merleau-Ponty, 1962; Parnas & Handest, 2003).

Moreover, disturbances of emotional responsiveness can also be accompanied by optical illusions of actual experience of bodily change, where patient either perceive changes of their own face or perceive changes in others' faces (Gross et al., 1992). This is known as *"Mirror-related Phenomena" (Spiegelphänomen),* where patients inspect their face in a mirror because of feelings of self-alteration or, alternatively, tend to avoid their mirror image, which is perceived as threatening or provoking (Parnas & Handest, 2003).

EASE scale describe the *"Mirror-Related Phenomena (…)* [as] *a group of phenomena,* [where] *(…) patients either perceive changes of their own face or they look for such changes, and therefore examine themselves in the mirror often and/or intensely. They become surprise or frightened by what they see, and even tend to avoid mirrors because of what they see. Sometimes they look in the mirror to assure themselves of their very existence. They might also look photos of themselves to find out about their own identity."* (Parnas et al., 2005, p.252).

Many evoking clinical cases and examples of this phenomenon are given by literature:

"When she looked at herself in the mirror, she focused on the eye, which she suddenly saw as a ball in her head. It was "surrealistic", and she felt that her face was changed". (Parnas et al., 2005, p. 252).

"Adam (…) saw faces as collections of individual features (nose, lips, etc.), rather than as unitary wholes. Adam explained: "it [referring to faces] wasn't expression, wasn't human anymore, I couldn't know whether somebody was annoyed or happy, they were disconnected parts." (Nelson & Sass 2009, p. 493).

"Suddenly patient (…) did not look beautiful and her side face was ugly. She used to watch the mirror for hours together. She got her face photographed from different angles and used to

compare them with the previous ones. She visited many plastic surgeons to get her side face improved by cosmetic surgery (…)." (Patel et al., 2004, p. 180).

A disjunction between one's subjectivity and bodily experience is frequently observed in SzSp conditions, particularly during the preonset or prodromal phase, as represented in many of the bodily basic symptoms, such as cenesthesias and impaired bodily sensations (Klosterkötter et al., 2001; Maggini & Raballo, 2004). An experiential distance hence emerges between the self and bodily experience, suggesting a tendency to experience one's body as an object, rather than an "inhabited" aspect of selfhood (Nelson & Sass, 2009). Consequently, as Stanghellini and Fusar-Poli (2012) argued, *"schizophrenic persons undergo a special kind of depersonalization: the living body becomes a functioning body, a thing-like mechanism in which feelings, perceptions, and actions take place as if they happened in an outer space.* [As a result,] *they also endure a special kind of derealisation/de-socialization: the interpersonal scene becomes like a theatre stage, pervaded with a sense of unreality, on which the main actor is anaware of the plot, out of touch with the role he is acting and unable to make sense of the objects he encounters and of what the people are doing."* (p. 338).

Embodiment is a fundamental condition of selfhood (Gallese and Sinigaglia 2010, 2011; Gallese and Ferri 2013; Stanghellini et al., 2012), and such *disembodiment of emotions* we found in our study, further remarks the need to conceptualize schizophrenia as a disorder of the S*elf* and of *Intersubjective attunement* (Stanghellini & Fusar-Poli, 2012).

In sum, in this study we explored the experiential correlates of emotional motor resonance occurring in Schizophrenia Spectrum patients. We found that a higher emotional motor resonance to negative stimuli is associated with patients' increased vulnerability and higher psychotic relapses. On the other hand, patients showing a higher emotional motor resonance toward positive stimuli, experienced increased emotional reactivity and possibly emotion disembodiment feelings resulting in self-detachment.

Noteworthy, a retrospective pilot study (Bechdolf et al., 2002) compared self-perceived prodromal subjective symptoms preceding relapses of schizophrenic and depressive patients, using BSABS scale. Interestingly, schizophrenic as well as depressive patients reported impaired tolerance to certain stress as subsumed in the BSABS-subsyndrome "vulnerability" (cluster 3) prior to their acute episode, whereas "increased emotional reactivity" (cluster 5) could be found significantly more often only in schizophrenic patients. Moreover, among the most frequent basic symptoms preceding schizophrenic relapses, BSABS A.7.2. (i.e., Disturbances of emotional responsiveness), was found to occur earliest before psychotic onset. Bechdolf et al. (2002) interpreted these prodromal symptoms as a complex of features possibly best described in terms of a "mild psychotic productivity" in the case of schizophrenia sample, whereas those also found in depressive patients were described in terms of "mild depressive syndrome". These results cohere with our findings, since an aberrant salience of negative emotional stimuli, possibly accompanied by some depressive feelings, could increase patients' vulnerability and hence facilitate psychotic relapse. On the other hand, a "mild psychotic productivity" could be recognizable in emotional responsiveness with respect to positive stimuli. Given its strict relation with emotions disembodiment and self-disintegration, the "mild psychotic productivity" could be thus possibly focused, in future psychopathological research, on the early detection of schizophrenia, since self-disturbances are acknowledged to be the core trait of schizophrenia psychopathology.

A possible limitation of this study, however, could be the relatively modest sample size and the lack of an exhaustive phenomenological exploration of self-disorders through the Examination of Anomalous Self-Experience (EASE) scale, which is specifically designed to examine SzSp patients' disorders of self awareness. Nevertheless, we believe that our present results represent a significant advance in research investigating physiological trait markers of susceptibility to schizophrenia. Most importantly, the results of our study strongly support the investigation of mirror neurons mechanism as a possible brain-level correlate of disturbed subjective experiences in schizrenia spectrum.

Further neurobiological studies should entail phenomenological-based investigations in a trans-domain approach, with the outstanding advantage of gaining unique insights into patients' experiential world. A first-person, phenomenological point of view, would enable cognitive neuroscience to explore the neurobiological underpinnings of schizophrenia, leading to a better understanding of patients' anomalous experience, and finally enabling to answer the question "what is it like to be a person with schizophrenia in the social world?" (Stanghellini & Fusar-Poli, 2012; Stanghellini & Ballerini, 2011).

References

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th edn.* Washington: The American Psychiatric Association.

Andreasen, N.C. (1984a). *Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City: University of Iowa.

Andreasen, N.C. (1984b). *Scale for the Assessment of Negative Symptoms (SANS).* Iowa City: University of Iowa.

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., and Ho, B.-C. (2010). Antipsychotic Dose Equivalents and Dose-Years: A Standardized Method for Comparing Exposure to Different Drugs. *Biol Psychiatry.* 67, 255–262.

Bechdolf, A., Schultze-Lutter, F., and Klosterkötter, J. (2002). Self-experienced vulnerability, prodromal symptoms and coping strategies preceding schizophrenic and depressive relapses. *Eur Psychiatry.* 17, 384–393.

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., and Lenzi, G.L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A.* 100, 5497–5502.

Catts, S.V., Fox, A.M., Ward, P.B., and McConaghy, N. (2000). Schizotypy: henotypic marker as risk factor. *Aust N Z J Psychiatry.* 34, s101–s107.

Chapman, L.J., and Chapman, J.P. (1987). The search for symptoms predictive of schizophrenia. *Schizophr Bull.* 13, 497–503.

Cronbach, L.J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrica.* 16, 297-334.

Derntl, B., Finkelmeyer, A., Voss, B., Eickhoff, S.B., Kellermann, T., Schneider, F., and Habel, U. (2012). Neural correlates of the core facets of empathy in schizophrenia. *Schizophr Res.* 136, 70-81.

Gallese, V. (2003). The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology*. 36, 171-180.

Gallese, V. (2005). Embodied simulation: From neurons to phenomenal experience. *Phenomenol Cogn Sci.* 4, 23-48.

Gallese, V. (2006). Intentional attunement: A neurophysiological perspective on social cognition and its disruption in autism. *Brain Res.* 1079, 15-24.

Gallese, V., and Sinigaglia, C. (2010) The bodily self as power for action. Neuropsychologia, 48: 746-755.

Gallese, V., and Sinigaglia, C. (2011) How the body in action shapes the self. J Consciousness Studies, 18: 117-143.

Gallese, V., and Ferri, F. (2013) Jaspers, the Body and Schizophrenia: The Bodily Self. Psychopathology, [Epub ahead of print ,2013 Jul 17]. DOI: 10.1159/000353258.

Gazzola, V., Aziz-Zadeh, L., and Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. *Curr Biol.* 16, 1824-1829.

Gross, G. (1989). The 'basic' symptoms of schizophrenia. *Br J Psychiatry*.155, S21–S25.

Gross, G., Huber, G., Klosterkötter, J., and Linz, M. (1992). *Scala di Bonn per la valutazione dei Sintomi di Base (BSABS)*. Pisa: ETS.

Handest, P., and Parnas, J. (2005). Clinical characteristics of first-admitted patients with ICD-10 schizotypal disorder. *Br J Psychiatry.* 48, s49–s54.

Heimann, H., and Spoerri, T. (1957). Das Ausdruckssyndrom der mimischen Düsintegrierung bei chronischen Schizophrenen. *Schweiz Med Wschrft*, 35/36, 1126-1132.

Hoffman, R. E., Woods, S. W., Hawkins, K. A., Pittman, B., Tohen, M., Preda, A., Breier, A., Glist, J., Addington, J., Perkins, D.O., and McGlashan, T. H. (2007). Extracting spurious messages from noise and risk of schizophrenia-spectrum disorders in a prodromal population. *The British Journal of Psychiatry*. 191, 355-356.

Huber, G. (1983). Das Konzept substratnaher Basissymptome und seine Bedeutung für Theorie und Therapie schizophrener Erkrankungen. *Nervenarzt.* 54, 23-32.

Huber, G. (1992). Konzeption der Einheitspsychose aus der Sicht der Basisstörungslehre. In C. Mundt, H. Sass (Eds), *Für und wider die Einheitspsychose.* (pp. 61–72). New York, Thieme Stuttgart.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psych.* 160, 13-23.

Klosterkötter, J., Ebel, H., Schultze-Lutter, F., and Steinmeyer, E.M. (1996). Diagnostic validity of basic symptoms. *Eur Arch Psychiatry Clin Neurosci.* 246, 147-154.

Klosterkötter, J., Gross, G., Huber, G., Wieneke, A., Steinmeyer, E., and Schultze-Lutter, F. (1997). Evaluation of the 'Bonn scale for the assessment of basic symptoms – BSABS' as an instrument for the assessment of schizophrenia proneness: A review of recent findings. *Neurol Psychiatr Brain Res.* 5, 137–150.

Klosterkotter, J., Hellmich, M., Steinmeyer, E.M., and Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry.* 58, 158–164.

Maggini, C., and Raballo, A. (2004). Subjective experience of schizotropic vulnerability in siblings of schizophrenics. *Psychopathology.* 37, 23–28.

Mass, R. (2000). Characteristic subjective experiences of schizophrenia. *Schizophr Bull.* 26, 921–931.

Merleau-Ponty, M. (1962). *The Phenomenology of Perception.* London: Routledge and Kegan Paul.

Møller, P., and Husby, R. (2000). The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. *Schizophr Bull.* 26, 217–232.

Molnar-Szakacs, I., Kaplan, J., Greenfield, P.M., and Iacoboni, M. (2006). Observing complex action sequences: the role of the fronto-parietal mirror neuron system. *Neuroimage.* 33, 923-935.

Molnar-Szakacs, I. and Uddin, L.Q. (2013). Self-processing and the default mode network: interactions with the mirror neuron system. *Front Hum Neurosci.* doi: 10.3389/fnhum.2013.00571

Nelson, B., and Sass, L.A. (2009). Medusa's stare: a case study of working with self-disturbance in the early phase of schizophrenia. *Clinical Case Studies.* 8, 489-504.

Nelson, B., Sass, L.A., and Skodlar, B. (2009). The phenomenological model of psychotic vulnerability and its possible implications for psychological interventions in the ultra-high risk ('prodromal') population. *Psychopathology.* 42, 283-292.

Nelson, B., Whitford, T.J., Lavoie, S., and Sass, L.A. (2013a).What are the neurocognitive correlates of basic self-disturbance in schizophrenia?: Integrating phenomenology and neurocognition. Part 1 (Source monitoring deficits). *Schizophr Res.* http://dx.doi.org/10.1016/j.schres.2013.06.022

Nelson, B., Whitford, T.J., Lavoie, S., and Sass, L.A. (2013b). What are the neurocognitive correlates of basic self-disturbance in schizophrenia?: Integrating phenomenology and neurocognition. Part 2 (Aberrant salience). *Schizophr Res.* http://dx.doi.org/10.1016/j.schres.2013.06.033

Nelson, B., Yung, A. R., Bechdolf, A., and McGorry, P. D. (2008). The phenomenological critique and self-disturbance: Implications for ultra-high risk ("prodrome") research. *Schizophr Bull.* 34, 381-392.

Niedenthal, P.M. (2007). Embodying emotion. *Science.* 316, 1002-1005.

Parnas, J. (2000). The self and intentionality in the pre-psychotic stages of schizophrenia: A phenomenological study. In D. Zahavi (Ed.), *Exploring the self: Philosophical and psychopathological perspectives on self-experience* (pp. 115-148). Amsterdam, Netherland: John Benjamins.

Parnas, J. (2003). Self and schizophrenia: A phenomenological perspective. In T. Kircher & A. David (Eds.), *The self in neuroscience and psychiatry* (pp. 127-141). Cambridge, UK: Cambridge University Press.

Parnas, J. (2005). Clinical detection of schizophrenia-prone individuals: Critical appraisal. *British Journal of Psychiatry-Supplementum.* 48, s111-112.

Parnas, J., and Handest, P. (2003). Phenomenology of anomalous self-experience in early schizophrenia. *Compr Psychiatry.* 44, 121-134.

Parnas, J., Handest, P., Jansson, L., and Saebye, D. (2005). Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology.* 38, 259–267.

Parnas, J., Handest, P., Sæbye, D., and Jansson, L. (2003). Anomalies of subjective experience in schizophrenia and psychotic bipolar illness. *Acta Psychiatr Scand.* 108, 126–133.

Parnas, J., Jansson, L., Sass, L.A., and Handest, P. (1998). Self-experience in the prodromal phases of schizophrenia. *Neurol Psychiatry Brain Res.* 6, 97–106.

Parnas, J., Møller, P., Kircher, T., Thalbitzer, J., Jansson, L., Handest, P., and Zahavi, D. (2005). EASE: Examination of Anomalous Self-experience. *Psychopathology.* 38, 236–258.

Parnas, J., and Sass, L.A. (2001). Self, solipsism, and schizophrenic delusions. *Philosophy, Psychiatry, & Psychology*. 8, 101-120.

Patel, A., Sharma, H., and Thakker, Y. (2004). Body dysmorphic disorder: an unusual presentation of schizophrenia. *Indian journal of psychiatry*. 46, 180.

Postmes, L., Sno, H.N., Goedhart, S., van der Stel, J., Heering, H.D., and de Haan, L. (2013). Schizophrenia as a self-disorder due to perceptual incoherence. *Sch Res.* http://dx.doi.org/10.1016/j.schres.2013.07.027.

Preston, S.D., and De Waal, F.B.M. (2002). Empathy: Its ultimate and proximate bases. *Behav Brain Sci.* 25, 1-20.

Raballo, A., and Parnas, J. (2011). The silent side of the spectrum: Schizotypy and Schizotaxic Self. *Schizophr Bull.* 7, 1017-1026

Raballo, A., Saebye, D., and Parnas, J. (2011). Looking at the schizophrenia spectrum through the prism of self-disorders: an empirical study. *Schizophr Bull.* 37, 344–351.

Sass, L.A., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr Bull*. 29, 427-444.

Schultze-Lutter, F., Klosterkoetter, J., Picker, H., Steinmeyer, E.M., and Ruhrmann, S. (2007a). Predicting first-episode psychosis by basic symptom criteria. *Clin Neuropsychiatry.* 4, 11–22.

Schultze-Lutter, F., Ruhrmann, S., Hoyer, C., Klosterkoetter, J., and Leweke, F.M. (2007b). The initial prodrome of schizophrenia: different duration, different underlying deficits? *Compr Psychiatry.* 48, 479–488.

Schultze-Lutter, F., Ruhrmann, S., Picker, H., von Reventlow, H.G., Brockhaus-Dumke, A., and Klosterkoetter, J. (2007c). Basic symptoms in early psychotic and depressive disorders. *Br J Psychiatry.* 51, s31–s37.

Seitz, R.J., Schäfer, R., Scherfeld, D., Friederichs, S., Popp, K., Wittsack, H.J., Azari, N.P., and Franz, M. (2008). Valuating other people's emotional face expression: a combined functional magnetic resonance imaging and electroencephalography study. *Neuroscience.* 152, 713-722.

Sestito, M., Umiltà, M.A., De Paola, G., Fortunati, R., Raballo, A., Leuci, E., Maffei, S., Tonna, M., Amore, M., Maggini, C. and Gallese, V. (2013). Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front Human Neurosci.* doi: 10.3389/fnhum.2013.00368.

Sonnby-Borgström, M. (2002). Automatic mimicry reactions as related to differences in emotional empathy. *Scand J Psychol.* 43, 433– 443.

Stanghellini, G. (2004). *Disembodied spirits and deanimated bodies: The psychopathology of common sense*. Oxford: University Press.

Stanghellini, G., and Ballerini, M. (2011). What is it like to be a person with schizophrenia in the social world? A first-person perspective study on schizophrenic dissociality–Part 2: Methodological issues and empirical findings. *Psychopathology*. 44, 183-192.

Stanghellini, G., Ballerini, M., Fusar Poli, P., and Cutting, J. (2012). Abnormal Bodily Experiences May be a Marker of Early Schizophrenia?. *Current pharmaceutical design*. 18, 392-398.

Stanghellini, G., and Fusar-Poli, P. (2012). The Vulnerability to Schizophrenia Mainstream Research Paradigms and Phenomenological Directions. *Current pharmaceutical design*. 18, 338-345.

Varcin, K.J., Bailey, P.E., and Henry, J.D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. *J Int Neuropsychol Soc.* 16, 621-629.

Wieneke, A., Schultze-Lutter, F., Steinmeyer, E.M., and Klosterkotter J. (1997). Abnormal subjective experiences and neuropsychological deficits in first-degree relatives of schizophrenics. *Schizophr Res.* 24, 49.

Chapter 5

5. General discussion and conclusions

The purpose of the first experiment, was to explore whether a possible multisensory disintegration would occur in patients with schizophrenia. To this aim, we tested a novel paradigm to investigate the evaluation of the emotional content of perceived emotions presented through dynamic expressive stimuli, facial mimicry evoked by the same stimuli, and their functional relation. Emotional facial expression, indeed, is an important low-level mechanism contributing to the experience of empathy, thereby lying at the core of social interaction. Noteworthy, schizophrenia is associated with pervasive social cognitive impairments, including altered emotional processing of facial expressions. Fifteen healthy controls and 15 patients diagnosed with schizophrenia were presented with stimuli portraying positive (laugh), negative (cry) and neutral (control) emotional stimuli in visual, auditory modalities in isolation, and congruently or incongruently associated. Participants where requested to recognize and quantitatively rate the emotional value of the perceived stimuli, while EMG activity of Corrugator and Zygomaticus muscles was recorded.

Results showed that all participants correctly judged the perceived emotional stimuli and prioritized the visual over the auditory modality in identifying the emotion when they were incongruently associated (Audio-Video Incongruent condition). The neutral emotional stimuli did not evoke any muscle responses and were judged by all participants as emotionally neutral. Control group responded with rapid and congruent mimicry to emotional stimuli, and in Incongruent condition muscle responses were driven by what participants saw rather than by what they heard. Patient group showed a similar pattern only with respect to negative stimuli, whereas showed a lack of or a non-specific Zygomaticus muscle response when positive stimuli were presented. Finally, we found that only patients with reduced facial mimicry (Internalizers) judged both positive and negative emotions as significantly more neutral than controls. This means that in patients with schizophrenia, facial mimicry in response to positive and negative emotions represents a crucial *bottom-up* process to correctly judge, from a dimensional point of view, the perceived emotion.

The aim of the second study was to investigate, on the other hand, a possible connection between phenomenological experience (i.e., the *mind* level) and physiological mechanisms (i.e., the *body* level), explored through the motor facial mimicry in response to emotional stimuli, previously demonstrated to be a mirror neurons mechanism *proxy* (Varcin et al., 2010; Carr et al., 2003). For this purpose, eighteen Schizophrenia Spectrum (SzSp) patients (comprising 14 patients with schizophrenia from previous study plus 4 patients with Schizotypal Personality Disorder) were tested with the same multimodal paradigm, in which positive and negative emotional stimuli were shown in different modalities while EMG activity of facial muscles was recorded. Abnormal subjective experiences were measured by means Bonn scale of basic symptoms (BSABS). BSABS items were then grouped following the composition of seven *a priori* scales described by Parnas and colleagues' work (Parnas et al., 2003). Correlations analyses were then performed between EMG facial reactions and BSABS scales. We found an imbalance in emotional motor resonance with a selective bias toward negative stimuli and single-sensory modalities in SzSp patients, which probably led them to a multisensory integration impairment. Most interestingly, we discovered a robust correlation between Self-disorders scale and EMG facial reactions in response to negative stimuli, presented only in auditory modality.

In the third study, we explored the experiential correlates of the emotional motor resonance occurring in SzSp patients, by dividing them in Externalizers (i.e., with higher emotional motor resonance) and Internalizers (i.e., with lower emotional motor resonance) for positive and negative emotions. We found that a higher emotional motor resonance to negative stimuli is associated with patients' increased vulnerability and higher psychotic relapses. On the other hand, patients showing a higher emotional motor resonance toward positive stimuli, experienced increased emotional reactivity and possibly emotion disembodiment feelings resulting in a self-detachment.

In conclusion, the primary aim of my thesis was to correlate the phenomenic, experiential aspects with the underlying physiological, motor facial mimicry-related mechanisms occurring in schizophrenia spectrum disorders, allowing a possible integration of findings belonging to

phenomenological and physiological levels of analysis, thus shedding new light on vulnerability to schizophrenia. The results of our studies strongly encourage research into mirror neurons mechanism as a possible brain-level correlate of disturbed subjective experiences in schizophrenia spectrum.

The discovery of mirror neurons promises to yield powerful insights into the neurobiology of disorders affecting the social brain (Iacoboni & Dapretto, 2006). These neurons fire during both action performance and action observation, thus providing a mechanism not just for recognizing actions but also for decoding the intentions underlying these actions (Iacoboni, 2009; Gallese, 2003; 2005; 2006). This mapping of the sensory representation of an action enables one to perceive the action of another as if he/she were performing that action himself/herself. Mirror neuron-driven embodied simulation has been proposed as a physiological basis of basic social cognitive abilities in humans (Gallese, 2007; Gallese & Sinigaglia, 2011). Empirical findings seem to support this theory (Tognoli et al., 2007), providing the first preliminary evidence of a significant association between certain social cognitive abilities and putative mirror neuron activity in patients with schizophrenia. These results, however, need to be replicated, especially in different schizophrenia spectrum conditions. In this view, deficits of mirror neurons mechanisms may be studied as putative neuro-markers of social cognition deficits in schizophrenia, given their possible association with Self-Disorders.

In conclusion, our multimodal experimental paradigm proved to be sensitive enough to successfully explore emotional motor resonance in response to different perceptual modalities and emotional valence. The paradigm employed in our studies could provide a useful framework to better understand perceptual incoherence, allowing to track disease susceptibility of high-risk individuals and improving recognition of early stages of schizophrenia. Indeed, schizophrenia is often preceded by sub-delusional detachment from reality that can be regarded as manifestation of self-disorders (Schultze-Lutter et al., 2010; Nelson et al., 2012; Parnas et al., 2011). Our paradigm, allowing the exploration of bodily motor resonance in response to different perceptual modalities

and emotional valence, might be a promising heuristic model to investigate multisensory disintegration and perceptual incoherence as possible early markers of schizophrenia, given their close connection with self-disorders, particularly in clinical asymptomatic, genetically high-risk individuals.

References

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., and Lenzi, G.L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A.* 100, 5497–5502.

Gallese, V. (2003). The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology* 36, 171-180.

Gallese, V. (2005). Embodied simulation: From neurons to phenomenal experience. *Phenomenol Cogn Sci.* 4, 23-48.

Gallese, V. (2006). Intentional attunement: A neurophysiological perspective on social cognition and its disruption in autism. *Brain Res.* 1079, 15-24.

Gallese, V., 2007. Before and below 'theory of mind': embodied simulation and the neural correlates of social cognition. Philos. Trans. R. Soc. Lond. B Biol. Sci. 362, 659–669.

Gallese, V., and Sinigaglia, C. (2011). What is so special about embodied simulation? *Trends Cogn. Sci.* 15, 512–519.

Iacoboni, M. (2009). Imitation, empathy, and mirror neurons. *Annu. Rev. Psychol.* 60, 653–670.

Iacoboni, M., and Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nat. Rev. Neurosci.* 7, 942–951.

Nelson, B., Thompson, A., and Yung, A.R. (2012). Basic self-disturbance predicts psychosis onset in ultra high risk for psychosis "prodromal" population. *Sch Bull.* 38, 1277-1287.

Parnas, J., Handest, P., Sæbye, D., and Jansson, L. (2003). Anomalies of subjective experience in schizophrenia and psychotic bipolar illness. *Acta Psychiatr Scand.* 108, 126–133.

Parnas, J., Raballo, A., Handest, P., Jansson, L., Vollmer-Larsen, A., and Sæbye, D. (2011). Self-experience in the early phases of schizophrenia: 5-year follow-up of the Copenhagen Prodromal Study. *World Psychiatry.* 10, 200-204.

Schultze-Lutter F, Ruhrmann S, Berning J, Maier W, and Klosterkotter J. (2010). Basic symptoms and ultrahigh risk criteria: symptom development in the initial prodromal state. *Schizophr Bull.* 36, 182–191.

Tognoli, E., Lagarde, J., DeGuzman, G.C., and Kelso, J.A. (2007). The phi complex as a neuromarker of human social coordination. *Proc. Natl. Acad. Sci. U. S. A.* 104, 8190–8195.

Varcin, K.J., Bailey, P.E., and Henry, J.D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. *J Int Neuropsychol Soc.* 16, 621-629.