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Neurophysiological processing of aberrant physical salience in schizotypy and schizophrenia

Dissertation

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„The poetic image is a sudden salience on the surface of the psyche“

Gaston Bachelard, *The Poetics of Space*

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1. Introduction

1.1 Objectives: Salience and visual perception

The Oxford English dictionary (2015) defines the adjective salient as „most noticeable or important“. The term originates from Latin „*salire“*, which means „to leap“, as in „to leap into someone’s mind“. Synonyms for „salient“ for the phrase: „the salient points stuck out clearly in her mind“ are e.g. „striking“, „key“, or „essential“. The term „*punctum saliens*“, (German: „der springende Punkt“) ascribed to Aristotle, exemplifies this meaning. Salience can refer to both, having experienced a perceptual object or an internal representation. In the psychology of perception, perceptual salience refers to physical low-level characteristics of a stimulus (e.g. intensive chromaticity), making the stimulus more eye-catching, as it leaps out from its surrounding (Tatler et al., 2011). The salience of perceptual stimuli guides fixation behavior and saccade execution facing a visual scene (Schütz et al., 2012; Rothkirch et al., 2013).

From a more comprehensive perspective, the nature of salience has been described scientifically by Phan et al. (2004). The authors present a categorization opposing exogenous and endogenous forms of salience. Exogenous salience refers to physical characteristics of a stimulus (e.g. bright color or loud noise) as pointed out above, whereas endogenous salience refers to responses towards a stimulus depending on appraisal. Further, endogenous salience is divided into generic salience of stimuli inheriting a general relevance as e.g. a 100 € bank note; or personal salience of stimuli, generated by personal emotional memories and subjective evaluation of stimuli, e.g. perceiving a gravestone after a beloved person has died. As will be revisited in section 1.5 and 1.6, the key aspect of salience for the experimental approach of the present thesis is exogenous salience. For reasons of simplicity exogenous salience will be referred to as physical salience in the following paragraphs.

1.1.1 The phenomenology of aberrant salience in schizophrenia

The term “aberrant” from Latin *“aberro”*, “to go astray”, describes something deviating from the ordinary, usual, or normal type. “Aberrant” is something exceptional or

abnormal. The concept of aberrant salience was introduced by Kapur (2003; 2005) as an approach to unite phenomenological, biological and pharmacological perspectives on schizophrenia. This phenomenon is addressed as a core experience in schizophrenia, underlying positive symptoms. Based on literature, Kapur suggests that the prominent dopamine excess in midbrain areas causes aberrant salience by its role in reward prediction and for the generation of motivational salience. Following this suggestion, psychosis might arise from aberrant assignment of novelty and motivational salience to objects and internal associations. Therefore, schizophrenia patients might experience excessive elicitation of prevalent ideas and meaning by random stimuli. Kurt Schneider (1959) distinguished delusional perceptions as a first-rank symptom from optical hallucinations. He conceptualized delusional percepts as a two-stage phenomenon of a normal perception followed by a delusional interpretation of special, highly personalized significance (Carpenter et al., 1973). Anscombe (1987) describes abnormal perceptions as filter disturbances in schizophrenia in an interesting approach citing phenomenal experiences by patients, e.g. from McGrath (1984):

> *"What is so „special"? Well, the times when colors appear brighter, alluring almost, and my attention is drawn into the shadows, the lights, the intricate patterns of textiles, the bold outlines of objects around me. It's as if all things have more of an existence than I do, that I've gone around the corner of humanity to witness another world where my seeing, hearing, and touching are intensified, and everything is a wonder."*

Regrettably, these earlier conceptualizations did not get much attention until very recently with their re-introduction by Kapur (2003, 2005) in relation to biological and pharmaceutical parameters. Since then, the concept of aberrant salience is becoming of growing relevance for research and clinical application in schizophrenia treatment. With reference to the discussion on the reformation of the DSM-V, Os (2009) suggested to replace the stigmatized diagnosis "schizophrenia" by the concept of the „salience syndrome". A main argument put forward in this discussion by Os, is the currently „misleading" and „mystifying" terminology, not relating to the core concepts underlying psychiatric nosology. According to Os, the salience syndrome has the potential to make the public recognize psychosis as relating to an aspect of human mentation and experience that is universal.

1.1.2 The role of perception for human cognition and experience

Perception of the surrounding world is based on the processing of physical input signals by sensory systems, e.g. by the visual system, or by the auditory system (Goldstein, 2014). Sensory information is processed by non-conscious (neural) processes (Dehaene & Changeux, 2011) providing information potentially available for conscious processing (Sperling, 1960). The psychology of visual perception examines the relation between a distal stimulus as an external entity and a proximal stimulus as its perceived internal representation (Goldstein, 2014). Importantly, both are not equivalent. Their inherent difference is remarkable, considering the complex mechanisms of deduction on the causing distal object, based on the sparse information obtained by the human retina. Several established approaches are concerned with this phenomenon.

An early suggestion by Helmholtz (1866) emphasizes experience as an important factor on the subjective view on the environment. Following his suggestion, human experience applies unconsciously for deductive reasoning on incoming perceptions. In familiar surroundings, this process promotes effective vision as only few contextual cues are necessary. In unknown situations whatsoever, this process may lead to false conclusions.

Another prominent approach on this topic is James J. Gibson's the ecological perception theory (1986). His central statement concerns the intentional quality of perception by a subject exploring options for action in the environment, relevant to the species. Natural environments hold different affordances for animate beings, shaping perception according to divergent potentialities.

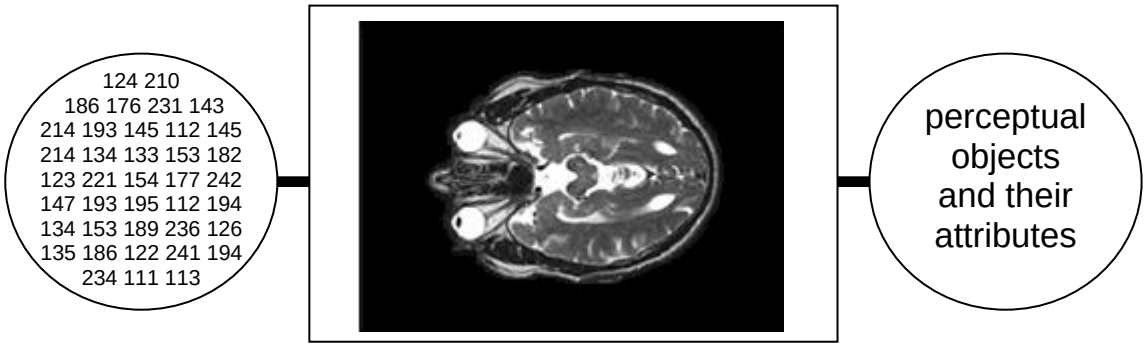

***Fig. 1**: The fundamental problem of perception: From distributions of physical energy on the retina to perceptual objects and their attributes, (Mausfeld, 2011)*

By addressing these matters of perception, the unresolved question on the origin of internal representations inevitably arises as a conflict between the idea of holistic perception and the existence of an innate representation of concepts, necessary for the interpretation of incoming sensory input (Mausfeld, 2011). It is still largely unclear how these internal structures might be implemented in biological parameters and how they can develop during childhood. As it is beyond the scope of this PhD thesis trying to resolve these types of questions, a fundamental premise to agree on here is that perception depends on retinal input and has a subjective component, which cannot be precisely specified. The application of abnormal perception processes in psychiatric conditions rather emphasizes the question which basic mechanisms are affected and in which way experiences may shape perception and cognition trying to find approaches how this could possibly be reversed.

1.2 Clinical considerations on salience perception

The German AMDP (2007), edited by the „Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie“, *(Engl: Consortium for methods and documentation in psychiatry)* is the standard manual for the documentation of mental diagnostic findings in German psychiatry. Therein, the criteria relevant to the clinical context of salience perception are [2.7] Delusion and [2.8] Hallucination. Interestingly, the phenomenon of salience perception, (AMDP, *German: „Wahnwahrnehmung“)*, is assigned to the superior criterion of delusions, while it is not classified with hallucinations. The AMDP (2007) defines delusions as a distorted appraisal of reality, which is hold on to with aprioristic and subjective certainty. Criteria for the content of delusions are: delusion of reference, delusion of persecution, delusion of jealousy, delusion of guilt, delusion of poverty, somatic delusion, grandiose delusion, and other delusions. Hallucinations are defined as false perceptions either without a causing external stimulus, or with a causing external stimulus, which is perceived as distorted (illusion). If a patient acknowledges the false perception as unreal, this is defined as a pseudo-hallucination. Hallucinations are further subdivided into hearing voices, other acoustic hallucinations, optical hallucinations, body hallucinations and odor / flavor hallucinations.

In contrast, delusional perceptions are defined as real perceptions, on which abnormal meaning is assigned, e.g. in the sense of self-relatedness without a rational or emotionally

comprehensible reason. The delusional perception is a delusional interpretation of a "real" perception. Importantly it should be questioned, which reasons can be considered as rational, emotionally comprehensible or pathological. A second question is, in which way this judgment depends on background knowledge and effort of the exploring clinician. For individual cases, differentiation between a delusional perception and a hallucinatory illusion may be subtle or overlapping, while aberrant salience should be identified as delusional perception referring to the AMDP (2007). An example for a delusional perception from the AMDP (2007) is a patient, noticing a dog looking at him lifting his paw and the patient interprets this as a godly revelation. Scientifically, it is of interest how the experience of „meaning" as a phenomenon emerges on the perceptual and on the neurophysiological level.

The AMDP is applied for the pathological description of clinical symptoms in psychiatric patients. Nevertheless, it is important to consider that a continuum exists in subclinical populations showing augmented forms of psychopathological symptoms.

For schizophrenia as a disorder, breaking out due to an interaction of genetic predisposition and environmental interaction, the endophenotype approach has been suggested to provide insights in pathophysiological mechanisms (Gottesman & Gould, 2003). Studies on healthy populations with either genetic or phenotypic overlap with schizophrenia are well suited to identify abnormal (neural) processes, presumably of relevance for schizophrenia. An advantage of this strategy is that healthy participants are less affected by side-effects of medication, superposition of different symptoms present in schizophrenia patients, or by cognitive and experimental overload.

Dimensional schizotypy is described as the accumulation of psychotic-like personality traits occurring within healthy participants and in the schizophrenia spectrum, qualitatively less severe than schizophrenia symptoms (Raine, 1991). Schizotypal personality has been shown to be influenced by additive genetic and unique environmental effects (Linney et al., 2003). Perceptual aberration in schizotypy have been found be highly correlated with magical ideation (Chapman et al., 1982).

1.2.1 Salience perception form a cognitive-behavioral perspective

Abnormal experience of stimuli from the cognitive-behavioral perspective is centrally linked with conditioning and learning. An internal psychological response arises, when a

representation is triggered by a stimulus. In the framework of classical conditioning, rules and relations of originally neutral stimuli (NS) and later conditioned stimuli (CS), presented together with unconditioned (e.g. threatening) stimuli (US) are assessed in order to explain conditioned reactions (CR) towards external stimuli. Experience is formalized regarding the co-occurrence of stimuli and the resulting behavior of an individual. Stimuli co-occurring more often, get more strongly associated (principle of frequency; Brown, 1820 cited from Mazur, 2006). The Rescorla & Wagner (1972) model deals with stimulus intensity (its salience) and expectation by a subject. The relation of expectation and the actual strength of a delivered stimulus strongly influence conditioning. Moreover, more salient NS drive faster conditioning, they get more easily conditioned (CS) than less salient stimuli. The framework of operant conditioning (Skinner, 1938) addresses acquisition and extinction of behavior, as shaped by reward and punishment. Stimuli, which are associated with reward or punishment, thereby become more salient. As pointed out in the paragraphs 1.3.2 and 1.4.2, a large branch of research on (aberrant) salience refers to this principle. In adaptation of the operant conditioning paradigm, the SORC model for cognitive-behavioral therapy (Kanfer, 2000) addresses micro-processes of behavior and thought, starting with an experienced stimulus. A stimulus (S) striking an organism (O) triggers a reaction (R), which is followed by a consequence (C) occurring with a specific contingency. Tendencies of thought and actions are also considered, allowing for detailed analysis of (delusional) perceptions and emerging (delusional) interpretations and their subjective consequences.

1.2.2 Salience perception from a schema therapy perspective

Abnormal perceptions also can be understood within the framework of schema therapy (Young et al., 2005), an account from the third wave of cognitive-behavioral therapy. A central assumption from schema therapy is that unconsciously built (emotional) schemata and their corresponding coping mechanisms affect behavior extensively. An unconscious influence of schemata on perception fostering contents of aberrant salience can be assumed. In this view, internal or external stimuli trigger ongoing experience, which is automatically influenced by personally specific existing schemata, provoking a pre-potent automatic reaction. This mechanism is potentially interesting for the understanding of delusional conclusions.

Conscious „top-down“ influences by rational thought and situational reappraisals, are assumed to partially inhibit the unconsciously operating schema-related processes (Roediger & Dornberg, 2011). Considering partially unconscious contributions on content and experience of aberrant salience may provide a useful approach in order to understand the psychological dimension of aberrant salience and delusion.

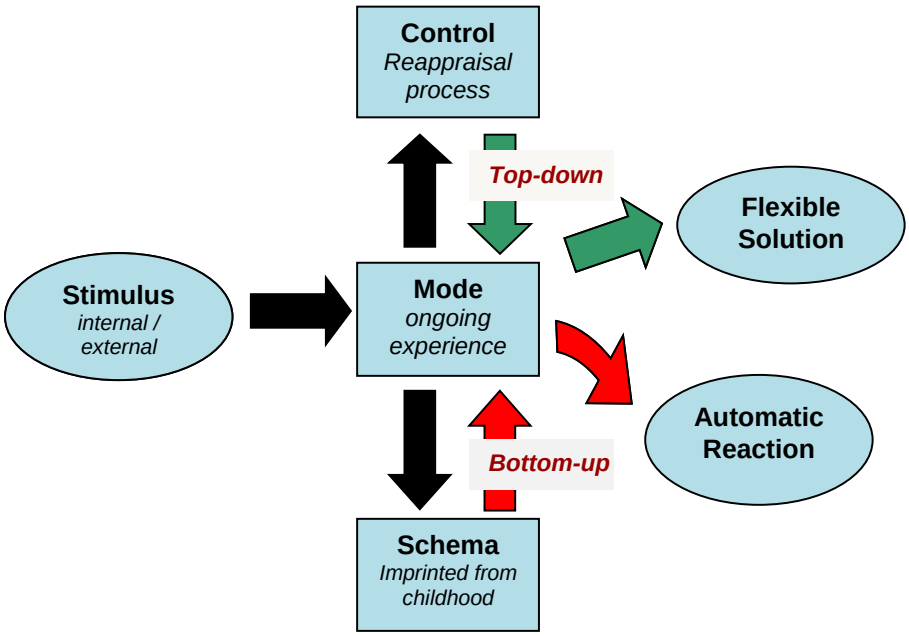

Fig. 2: *Model on the regulation of behavior in schema therapy (Roediger, 2011)*

1.2.3 Salience perception from a psychodynamic perspective

Despite many weaknesses regarding scientific foundation of psychodynamic approaches, several conceptualizations deserve recognition for the topic of aberrant salience perception and delusions. The psychodynamic perspective distinguishes between factual outer reality, such as workplace and domestic circumstances and the dynamically active inner reality, comprising perception of reality and the attitudes towards it. Outer reality and inner reality are considered to be closely entangled (Schnoor, 2011). Elements from outer reality can be introjected as inner reality „the outside in the inside“. Outer reality includes projected elements from the inside „the inside in the outside“ (Schmidt, 2008). Phenomenological, delusional perceptions can be regarded as such a phenomena. This conceptualization of a partly permeable psychic boundary between the representations of

internal and external reality is a remarkable observation (Teising, 2005), though it may not be scientifically provable. For psychotic patients it is assumed that loss of control in keeping inner and outer reality separate yet interrelated, constitutes a key difficulty. Increased permeability of a "leaky" boundary in psychosis may result in increased responsiveness to (salient) external stimuli. Freud (1940) hypothesized this boundary as a „contact-barrier", assuming a cortical layer equipped with organs for receiving stimuli and simultaneously forming a neuronal barrier as protective shield against stimuli. Partly, this conceptualization resembles modern conceptualizations of neuronal signal transmission described in the paragraphs 1.5 - 1.5.4. Preventing stimuli referring to (unconscious) conflicts from entering conscious processing is a defense mechanism (Freud A., 1936). This means that a healthy psyche shields from conflict-related information. This so-called „perceptual defense" has been reformulated by Erdelyi (1974) in terms of information processing approaches resulting in higher recognition thresholds for conflict-related stimuli. It is opposed with the perceptual vigilance effect, referring to a relative lowering of recognition thresholds for emotional stimuli. The breakdown of normal defense mechanisms, as assumed for psychotic patients, might result in lowering of recognition thresholds for conflict-related stimuli, phenomenologically experienced as aberrant salience.

1.3 The relation of aberrant salience and delusion in schizophrenia

Delusions as a core symptom of schizophrenia are of central interest for clinical research. The presence of a delusion often is not easily ascertained without ambiguity. A multidimensional characterization of delusions by Oltmanns (1988) proposes seven dimensions which, taken together, make it more plausible to declare a person's subjective belief a delusion. This is if the delusion (is)… 1. unfounded 2. firmly held 3. resistant to change 4. preoccupying 5. distressing 6. interferes with social functioning 7. involves personal reference. In the beginnings of psychiatry in Europe, the view on delusion formation was formed by phenomenological approaches. Mishara & Fusar-Poli (2013) retrace the work of the German psychiatrist Karl Jaspers, who emphasized the naïve realism as origin for odd beliefs in the delusion formation process. The naïve realism of everyday life suggests that what one sees and experiences is real, it is the uncritical perspective of the world, as experienced immediately through the senses. Therefore,

unusual perceptual experiences are prone to consolidate delusional convictions. Further, it is argued that the limits in understanding this primary delusional experience from the perspective of the clinician, has caused the still existing dogma of the non-understandability of a delusion. Mishara & Fusar-Poli (2013) assume that this is a reason why the level of explanation for delusions progressively shifted away from the patients' original subjective experience towards physical medicine. In order to overcome this separation, it is argued for a person-centered medicine considering both, the medical and psychological level.

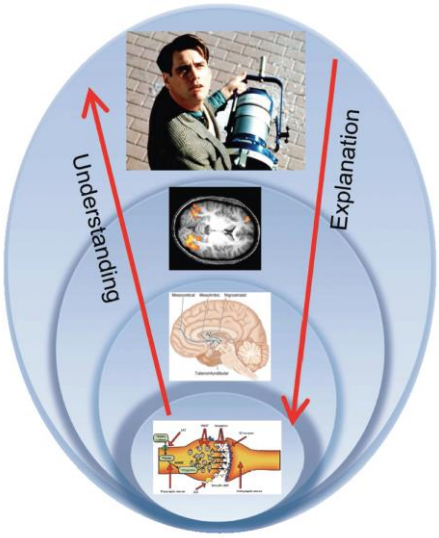

Fig. 3: *Understanding delusion formation (Mishara & Fusar-Poli, 2013)*

This is also important in order to give a comprehensible scientific explanation for subjective experiences. Modern cognitive approaches providing models on the formation of delusions, are becoming increasingly important. The prominent cognitive model by Freeman (2007) on the generation of delusions encompasses the three interdependent factors of emotional beliefs, anomalous experiences and cognitive biases. Central to this cognitive model are anomalous experiences of patients, which are assumed to cause delusional thinking in a search for meaning. A personal explanation for odd experiences is created in the experience-based delusion. Freeman (2007) continued work from Hemsley (1993) and Garety et al. (2001) going back to the proposal put forward by Maher (1974) that the paranoid reactions of many schizophrenia patients should be seen as a normal, „sane" reaction by an individual, arising from abnormal perceptual

experience. At present, the three factors from the Freeman model are partially supported, empirically. Empirical evidence for the cognitive biases of „jumping to conclusions“ (JTC) is relatively well established (Lincoln et al., 2010), while other biases are less well explored. Garety & Freeman (1999), reviewed evidence for cognitive biases in addition to JTC, which are externalizing attribution biases and deficits in understanding social situations and the intentions of others, also termed „theory of mind“ (ToM) abnormalities. The role of arousal and emotional beliefs (Freeman et al., 2001) still need further specification and evidence. Recently, Freeman et al. (2013) could show in support of their model, that experimental induction of worry increased mild anomalous experiences including feelings of unreality, temporal disintegration and, as relevant to the present topic, perceptual alterations. Importantly, the exact nature and the biological causes of anomalous experiences still need to be explored in detail, which is one of the goals of the present thesis.

1.3.1 The perception-prediction model of aberrant salience

Fletcher & Frith (2008) put forward that a successful explanation of positive symptoms needs to work at the three levels of 1) subjective experience 2) cognitive processes and 3) neural processes, referring to one another. In the perception-prediction model, they advance the hypothesis that abnormal perceptions and abnormal beliefs might be part of the same process, not in need to be considered separately. It is argued that the principle of prediction and learning is relevant to both, abnormal perception, as well as formation of beliefs, which is suggested to be disrupted in schizophrenia. It is put forward, that prediction in perception is important, as internal action produces predictable experiences, while changes in the external world produce widely unpredictable experiences. Normally, own movement and speech are highly predictable and their sensory consequences are therefore dampened (Heinks-Maldonado et al., 2005). In contrast, sensory experience can occur unpredicted and hence is not suppressed. Auditory hallucinations are assumed to arise from misattribution of inner speech to an external source. Disrupted motor-sensory communication may lead to a failure in prediction-based attenuation in schizophrenia, causing difficulty in distinguishing internally from externally generated stimuli. (This resembles the phenomenal psychodynamic description

of a disrupted distinction between outer and inner reality in schizophrenia, described in paragraph 1.4.3).

Beyond perception, Fletcher & Frith (2008) argue that prediction is also important for the relational processing of external stimuli. They pronounce that it is a process of learning, when and where stimuli will arise and which other stimuli they are likely to occur with, also in the sense of cause and effect. Thus, the predictability of a perceived stimulus-pair depends on prior knowledge. It is stated that prior knowledge affects how external stimuli are experienced at a basic sensory level, as they put it: „each experience is affected by what one believes“ (Fletcher & Frith, 2008). This idea goes back to the theory of Helmholtz as marked in paragraph 1.1.2, expanded with cognitive-behavioral approaches, described in paragraph 1.2.1. For example, the expectation of stimulus strength in contrast to delivered stimulus strength (its salience) already was considered as relevant for processes of learning by Rescorla & Wagner (1972). The new computational basis as Bayesian inference theory, has been proposed as basic principle of brain organization (Lee et al., 2003; Friston et al., 2006; 2014; Summerfield et al., 2008). Friston et al. (2014) provide a hierarchical model for brain functioning, encompassing low-level and high-level interdependence of subsystems: A low-level (sensory) prediction error, associated with activity of superficial pyramidal cells, would influence higher-level (cognitive) systems, updating perceptual inferences associated with activity of deep pyramidal cells. A sensory prediction-error alerts the organism, grabbing attention as an unexpected change in the environment, ensuing new inferences. The violation of an expectation evokes the occurrence of greater attention, making a stimulus more salient and perhaps more associable. Due to this interaction of perception and beliefs in a recursive loop, abnormal perception may furnish abnormal beliefs about the world and abnormal beliefs can cause abnormal perceptions in schizophrenia. This hypothesis by Fletcher & Frith (2008) refines and expands the relation of perception and belief in schizophrenia, also forwarded in the Freeman model, described in paragraph 1.3. The Bayesian principle that knowledge and believes are updated when new (perceived) experiences add to this, suggests an interaction of experience and belief. Adequate integration of previous knowledge with new experiences is assumed to be disrupted in schizophrenia patients (Hemsley, 2005).

1.3.2 The reward model of aberrant salience

The reward model of aberrant salience promotes the idea that dopaminergic neuronal firing in the reward system is increased in schizophrenia patients, causing aberrant salience of random stimuli (Kapur, 2003; 2005). Maladaptive attribution of importance to innocuous stimuli is assumed to cause abnormal referential ideas. The reward system (Haber & Knutson, 2010) encompasses several brain structures including the ventral striatum, the ventral pallidum, anterior cingulate cortex (ACC), the orbital prefrontal cortex (OFC) and the midbrain dopamine neurons. Also further structures, such as the dorsal prefrontal cortex, amygdala, hippocampus, thalamus, lateral habenular nucleus, and specific brainstem structures such as the pedunculopontine nucleus and the raphe nucleus are involved in regulating the reward circuit depicted in fig. 4.

Berridge et al. (2012) review the psychological distinguishable components of incentive salience of learning (e.g. reinforcement, association and prediction error), incentive motivation and pleasure. All of these are of potential interest to symptom formation in schizophrenia, though presumably by separate ways. The dopamine hypothesis in its revised form explains positive symptoms with hyper-activation of the mesolimbic dopamine system, including the striatum and the nucleus accumbens via D2-receptors. Negative symptoms are explained with hypo-activation of the mesocortical system (projections to the prefrontal cortex [PFC]) via D1-receptors (Guillin et al. 2007). While the role of the dopamine systems has been implicated in causation of schizophrenia symptoms for a long time, the question of how specific symptoms arise, remains widely unanswered. Research is aimed at relating the role of dopamine neurons and specific sub-functions of the reward system with schizophrenia symptoms (Murray et al. 2008).

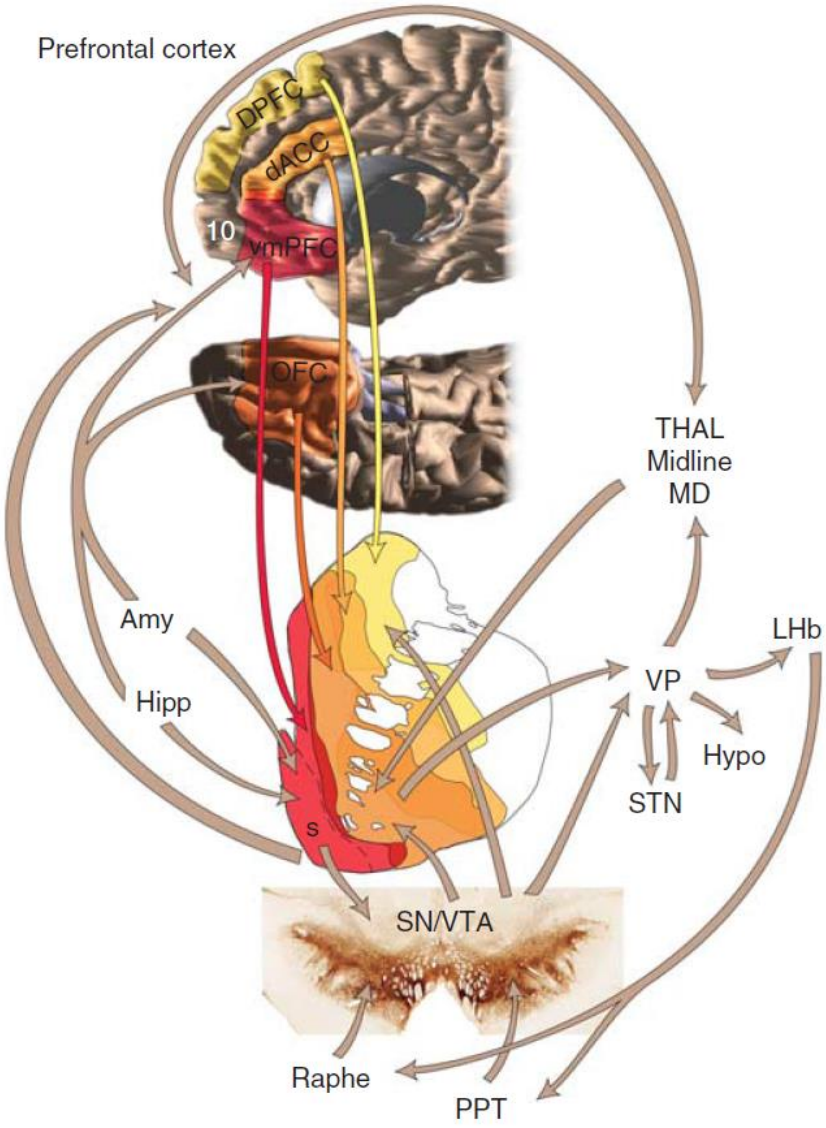

Fig. 4: *Schematic key structures of the reward circuit (Haber & Knutson, 2010). Red arrow = input from the vmPFC; dark orange arrow = input from the OFC; light orange arrow = input from the dACC; yellow arrow = input form the dPFC; brown arrows = other main connections of the reward circuit. Amy = amygdala; dACC = dorsal anterior cingulate cortex; dPFC = dorsal prefrontal cortex; Hipp = hippocampus; LHb = lateral habenula; Hypo = hypothalamus; OFC = orbital frontal cortex; PPT = pedunculopontine nucleus; S = shell, SN = substantia nigra, pars compacta; STN = subthalamic nucleus.; Thal = thalamus; VP = ventral pallidum; VTA = ventral tegmental area; vmPFC = ventral medial prefrontal cortex.*

1.3.3 The attention model of aberrant salience

A third account, which was applied very recently on schizophrenia, relates to the selection of perceptual input for conscious perception via neuronal attention networks. The selection of stimuli is assumed to be regulated via two anti-correlated networks: The central executive network (CEN) involved in the generation of goal-directed attention, and the default mode network (DMN) assumed to identify behaviorally relevant, salient stimuli as an alarming „circuit-breaker" of the CEN (Corbetta & Shulman, 2002).

The CEN or „dorsal frontoparietal network", comprises parts of the intraparietal cortex (intraparietal sulcus and superior poster lobule) and the frontal eye field. These regions of the CEN show increased metabolic activity during experimental settings, in which visual cues are presented, indicating a direction or goal feature, on which attention should be directed (Corbetta et al., 2000; Astafiev et al., 2003; Shulman et al., 1999; Hopfinger et al., 2000; Corbetta et al., 2005; Giesbrecht et al., 2003).

The DMN or "ventral frontoparietal network" is largely lateralized to the right hemisphere and encompasses the right temporoparietal junction (TPJ) and ventral frontal cortex (Corbetta & Shulman, 2002). The DMN shows increases in activity during the detection of salient stimuli, especially at unexpected positions (Corbetta et al., 2000; Astafiev et al., 2003; Kincade et al., 2005). Activity within the CEN and the DMN is negatively correlated with each other, also in resting-state analyzes without stimulus presentation (Fox et al., 2006).

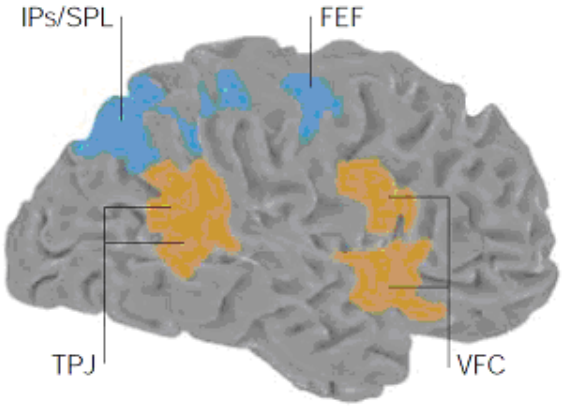

Fig. 5: *The central executive network (CEN) in blue: intraparietal sulcus (IPs)/ superior parietal lobule (SPL) and frontal eye field (FEF). Default mode network (DMN) in yellow: temporoparietal junction (TPJ) and ventral frontal cortex (VFC), (Corbetta & Shulman, 2002)*

Importantly, the specific functions and sub-nodes of the DMN are not yet sufficiently understood (Laird et al., 2009). In general, activity of the DMN is the state of the brain during stimulus independent thought, serving a variety of functions (Raichle & Snyder, 2007; Mason et al., 2007; Spreng & Grady, 2009). The right TPJ consistently has been found to be active in both of the two cognitive domains of attention and social cognition. Bzdok et al. (2015) could show that increased activity in the anterior cluster, together with a midcingulate-motor-insular network, is associated with attention, while decreased activity together with a parietal network is associates with social cognition and memory.

The question on the regulation and switching between the ventral and dorsal frontoparietal attention networks might yield an important account on the occurrence of aberrant salience in schizophrenia. Palaniyappan & Liddle (2012) suggest that the salience network (SN), consisting of bilateral insula and dorsal anterior cingulate cortex (White et al., 2010) enables adequate switching between CEN and DMN attention modes. They hypothesize the SN to mediate internal „proximal salience“ of evaluated external sensations, bodily sensations or stimulus independent thought, updating internal expectations. Hence, dysfunction of the SN in patients with schizophrenia is assumed to cause self-generated internal processes to be experiences as proximal very salient. Abnormal proximal salience is hypothesized to cause abnormal recruitment of the DMN in schizophrenia patients, inhibiting its normal suppression during tasks requiring an external focus of attention. This model provides a view on the emergence of aberrant salience and hallucinations, understood as self-generated externalized speech (McGuire et al., 1995).

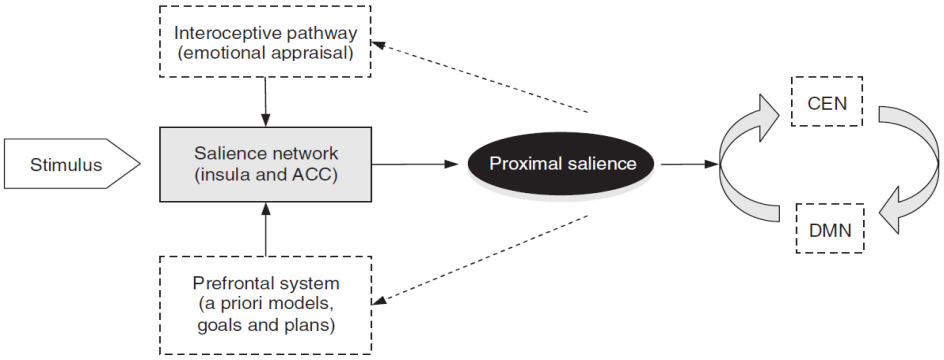

Fig. 6: *Schematic model on the salience network (Palaniyappan & Liddle, 2012)*

1.4 Neuroimaging of aberrant salience with fMRI

Research in neuroscience using functional magnetic resonance imaging (fMRI) for studying brain function is a rapidly growing field. This noninvasive technique is applied in order to localize changes of cerebral blood flow in 3D measurements of the brain. Thereby, neuronal activity is quantified indirectly by assessing the blood flow, compensating for the energy demand of active neurons in the measured brain regions (Raichle, 1998). The effect captured by fMRI is the blood oxygen level-dependent (BOLD) contrast, localizing changes in brain oxygen consumption accompanying neuronal firing. For measuring the BOLD effect, a strong magnetic field is generated in the fMRI scanner and the resulting spin-off effect of hydrogen (H+) atoms is obtained for construction of the 3D image. Since the discovery of Ogawa et al. (1990) showing that hemoglobin has different magnetic properties in its oxygenated and deoxygenated forms, i.e. in its arterial and venous form, the BOLD has been established to study the relationship of oxygen consumption based on the metabolic changes of hemoglobin in the brain. This method is widely applied providing a good spatial resolution enabling prosperous research on neural processes.

1.4.1 Evidence for the perception-prediction model

Experimentally, the nature of active selection and interpretation of sensory information is difficult to capture. Sterzer et al. (2009) reviewed approaches on multi-stable perception and the emergence of perceptual awareness of sensory stimuli in healthy participants. For schizophrenia, evidence supporting the assumptions from the perception-prediction model is still sparse. Sanders et al. (2012) did not find a behavioral difference in a paradigm for the detection of predictable and unpredictable targets in schizophrenia patients, though patients with paranoid schizophrenia showed stronger interference with motion representation.

A recent fMRI study by Schmack et al. (2013) provided first evidence for the perception-prediction model, as delusional ideation in healthy participants was associated with less perceptual stability towards ambiguous stimuli. Moreover, a stronger belief-induced bias on perception was associated with biased belief-congruent perception of ambiguous stimuli on the behavioral and neural level. Also the belief-induced bias on perception was

paralleled by enhanced functional connectivity between orbitofrontal areas encoding beliefs, and sensory visual areas encoding perception. These findings are remarkable, elegantly showing an effect of expectation on perception.
Nevertheless, the important postulated effect of the sensory prediction-error on beliefs is not supported experimentally by these results. Moreover, their finding was obtained in healthy participants only, not allowing for generalization on patients with schizophrenia.

1.4.2 Evidence for the reward model

Evidence for the reward model clearly is quite numerous, though relatively diverse. Many findings do not find relevant activation in the midbrain regions of the reward system, but report associations of positive or negative symptoms with frontal regions, tapping different aspects of dysfunctional (reward) processing in schizophrenia.
Evidence for the midbrain regions of the reward system being involved in aberrant salience processing as suggested by (Kapur, 2005) so far comes from three studies referred to at the end of this paragraph, applying physically salient but neutral stimuli within a reward context.
A finding by Juckel et al. (2006) assessed the anticipation of gain and loss, reporting reduced ventral striatal activation during the presentation of reward-indicating cues in schizophrenia patients. Reduced activity this region was negatively correlated with the severity of negative (not positive) symptoms, thus not supporting the motivational hypothesis of aberrant salience by Kapur (2005).
Other investigations aiming at the reward system found activations in frontal cortex during reward processing, showing associations with positive symptoms. Hypo-activation in the ACC of schizophrenia patients was negatively correlated with positive symptoms in a paradigm with monetary reward expectation, while activation in the ventral striatum, coding gain and loss, did not differ significantly between schizophrenia patients and healthy controls (Walter et al., 2009). Similar negative correlations of frontal regions with positive schizophrenia symptoms in reward paradigms were found in medial PFC by Schlagenauf et al. (2009) and OFC by Rothkirch et al. (2012). These findings did not find relevant activation in the midbrain regions of the reward system, possibly rather suggesting a role of abnormal (attentional) regulation of these processes in schizophrenia.

Walter et al. (2010) found measures of ventrolateral PFC to be inversely correlated with negative symptoms, thereby also not supporting the Kapur (2005) hypothesis.

Murray et al. (2008) showed that the magnitude of the neural response in the reward system for the reward-prediction error was diminished for reward trials in schizophrenia patients, while it was increased for neutral trials. The authors interpreted this finding in the way that patients failed in making the distinction between motivationally salient and irrelevant events on the neural level. This result also yields the assumption that aberrant processing of neutral items may be more important that the reward context. An association with schizophrenia symptoms was not reported in their study.

A recent study by Roiser et al. (2013) assessed the relation of delusions with neural responses to relevant and irrelevant stimulus features within a conditioned reward paradigm. Individuals at ultra-high risk for psychosis exhibited a tendency to rate irrelevant cue features as being more associated with reward than healthy control participants did. This bias correlated with the severity of delusion-like symptoms in the ultra-high risk group. Ventral striatal responses to the irrelevant stimulus features were correlated with delusion-like symptoms in the ultra-high risk group. The irrelevant stimuli used in the study were the same physically salient stimuli as the reward-predicting stimuli, but of another color.

A comparable study by Jensen et al. (2008) assessed abnormal functioning of the reward system in schizophrenia in relation to aversive conditioning. They found increased activation in the ventral striatum in response to neutral stimuli in schizophrenia patients. Their result is displayed in fig. 7. Also in the study by Jensen et al. (2008), the neutral stimuli were (unconditioned) physically salient stimuli of another color as the motivationally conditioned stimuli. This finding also was interpreted as impairment in the ability to distinguish between neutral and emotionally salient stimuli in schizophrenia patients.

These findings are in consistence with the hypothesis that patients assign aberrant motivational salience to neutral stimuli, processed in the midbrain (Kapur 2003, 2005). Nevertheless, the role of attention appears to be of relevance, also in the reward context. Physical stimulus salience may have an important role on stimulus evaluation as well, possibly accounting for the problem in distinguishing between neutral and emotionally salient stimuli in the experiments by Jensen et al. (2008) and Roiser et al. (2013).

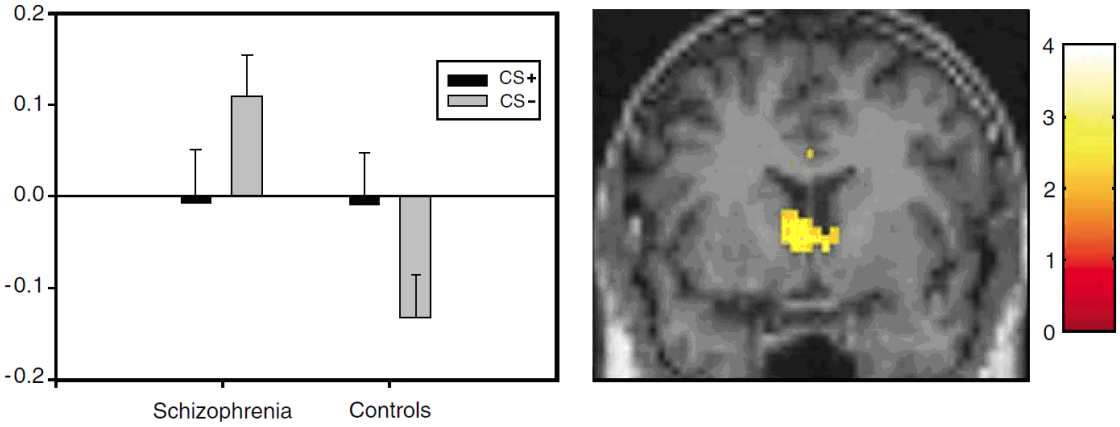

Fig. 7: *Aberrant responding in the reward system towards motivationally unconditioned (neutral) physically salient stimuli in schizophrenia patients and matched healthy control participants (Jensen et al. 2008)*

1.4.3 Evidence for the attention model of aberrant salience

Regarding the attention model of aberrant salience by Palaniyappan & Liddle (2011) on the role of the salience network (SN) in schizophrenia as described in paragraph 1.3.3, Sridharan et al. (2008) showed in healthy participants, that activation of the anterior insula temporally preceded activation in goal-directed networks. Also, findings on abnormal activation of the SN regions in schizophrenia patients exist, showing abnormal insula activation with a deficiency of cingular activity (Sommer et al., 2008). Increased activity of the anterior insula was found during auditory hallucinations in schizophrenia patients across several studies (Jardri et al., 2011). Diminished activation in the ACC has been found in schizophrenia patients during active maintenance of working-memory (Henseler et al., 2009), in ACC and insula during error-monitoring (Polli et al., 2008) and during attention on somatosensory stimuli (White et al., 2010). In the latter study, also reduced co-activation between Insula and ventromedial frontal cortex, which is part of the DMN, was observed in patients with schizophrenia.

Furthermore, it was shown, that patients with schizophrenia and their healthy relatives have difficulties deactivating the DMN in resting-state tasks (Garrity et al., 2007; Skurdlarski et al., 2010). These very interesting findings support the view of a relevant role of the SN and the DMN in schizophrenia, while the exact causal pathway, as suggested by Palaniyappan & Liddle (2011) requires further evidence. Also, direct evidence for abnormal processing of salient input in the DMN of schizophrenia patients,

which is the core assumption for the emergence of aberrant salience via these networks, still is missing.

1.5 Neuroimaging of cognitive and perceptual processes with EEG

The Electroencephalogram (EEG) is used since the beginning of the 20th century for research on abnormal brain functions. For this non-invasive technique, multiple recording electrodes are applied on a subject's scalp, measuring voltage fluctuations resulting from ionic currents within large population of neurons, firing synchronized. Detectable electrical waves are created by the ion field summation of neurons with a similar spatial orientation. Pyramidal cortex neurons are assumed to account for most of the EEG signal, as they are spatially aligned in layers firing together (Zoschke, 1995). In comparison to fMRI, the EEG is less precise regarding the localization of brain activity in specific regions, but the temporal resolution of the rapidly changing neuronal signals can be recorded much more exactly. The event-related potential (ERP) obtained at the scalp is assumed to consist of a superposition of evoked oscillations in different frequencies, ranging from delta to gamma ("natural frequencies of the brain") such as delta [0.5-3.5 Hz], theta [4-7 Hz], alpha [8-13 Hz], beta [15-28 Hz] und gamma [30-70 Hz] (Basar et al., 2013). Current research is aimed at linking oscillatory activity within the different frequency bands with neuronal generators and specific brain functions. Especially gamma oscillations have become increasingly relevant for research in schizophrenia, as their neurophysiological basis described in paragraph 1.5.3, might yield important insights into related disrupted neurotransmitter systems and disease-related disturbances. So far, there were no investigations assessing gamma-related brain functions in the context of aberrant salience.

1.5.1 The P50 and mismatch-negativity (MMN) in schizophrenia

Research on evoked potentials in schizophrenia identified two mechanisms, which could be related to aberrant salience in schizophrenia, as suggested by Nelson et al. (2014).
The first mechanism is mismatch negativity (MMN), referring to changes in brain activity in response to the occurrence of novel, unexpected auditory stimuli, causing an attentional shift (Näätänen & Kähkönen, 2009). Generation of the MMN was related to

functioning of the NMDA receptors, as NMDA antagonists were shown to block the generation of MMN (Javitt et al., 1996). A reduction of MMN amplitude in response to oddball stimuli was reported for schizophrenia patients (Umbricht & Krljes, 2005). While this impairment occurs as a function of illness duration, abnormalities revealed by a deficient temporal MMN generator process might be associated with patients' positive symptoms. Attenuated responses of the frontal MMN generator, might contribute to the negative symptoms (Näätänen & Käkhonen, 2009).

The second mechanism is the P50 potential, a measure of the sensory gating process obtained with auditory dual-click paradigms. Normally, the P50 amplitude of the positive potential occurring approximately 50 ms post-stimulus for the second click in pair-wise presentation is decreased. This so-called sensory-gating effect is assumed to reflect a protection against information overload, (a conceptualization similar to Freud's idea on the „contact barrier", described in paragraph 1.2.3). In schizophrenia patients, abnormal auditory gating has been observed (Bramon et al. 2004; Patterson et al. 2008) as a decreased attenuation of the P50 amplitude for the second click. These findings can be interpreted in the way, that these patients cannot inhibit irrelevant sensory input, causing an overload of information reaching the brain and contributing to deficits in perception and attention in schizophrenia (Nelson et al. 2014).

1.5.2 Gamma oscillations in cognitive and perceptual processes

Oscillatory synchronization of neuronal assemblies in the gamma frequency range is recognized to be strongly associated with sensory and perceptual processes (Jensen et al., 2008). Furthermore, cognitive functions related to memory (Lenz et al., 2007) and feature-binding (Tallon-Baudry et al., 1996) have been associated with neural oscillations in the gamma frequency range. Sensory processing of stimuli in different modalities, as in the olfactory (Beshel et al., 2007), auditory (Schadow et al., 2007) and visual (Demiralp et al., 2007) domain, is accompanied by gamma oscillations. An earlier review by Basar-Eroglu et al. (1996) on gamma oscillations provides an historical overview on this field of research. A more recent review by Herrmann et al. (2010) encompasses an integrative view, proposing that different cognitive (sub-) functions can be united in one conceptual framework regarding gamma oscillations. It is proposed that binding of multiple perceived object features requires a comparison with contents stored in memory.

Following the “match-and-utilization model” (Herrmann et al., 2004) the comparison of memory contents with stimulus input is reflected in the early evoked visual gamma-band response.

[figure 8 left blank due to missing copyright]

Fig. 8: *The match-and-utilization model depicts the “match” function of stored memory contents with perceived object features by the early gamma-band-response (GBR) (Herrmann et al., 2004)*

Fries (2009) puts forward that neuronal gamma-band synchronization, as found in many cortical areas and in relation to different stimuli or tasks, may result from one fundamental process of cortical computation. It is suggested that the relation between neuronal synchronization and neuronal interaction generally is implemented via gamma oscillations, enabling exclusive neuronal communication links.

For the visual modality, evoked gamma-band responses (GBR) in occipital areas have been shown to depend on physical features of an external stimulus, with larger stimuli producing a stronger GBR (Busch et al., 2004). Beyond, it was also shown that the early visual evoked GBR can be enhanced by allocation of attention (Herrmann & Mecklinger, 2001; Busch et al., 2006).

1.5.3 Gamma oscillations in schizophrenia

Research on gamma oscillations is central to the pathophysiology of schizophrenia (Uhlhaas & Singer, 2010). However, the exact nature of gamma-related aberration in schizophrenia patients across divergent measures and tasks, is not sufficiently well understood. Inconsistent results on alterations of sensory evoked gamma oscillations in

schizophrenia require further clarification. For the auditory domain, the early evoked GBR as assessed in auditory processing was found to be reduced in schizophrenia patients (Leicht et al., 2010), as well as in healthy siblings of schizophrenia patients (Leicht et al., 2011) and also in healthy twins of schizophrenia patients (Hall et al., 2011). Based on these results, the reduced auditory evoked GBR at 40Hz in auditory paradigms with a top-down focus was proposed as an endophenotype for schizophrenia. A decrease of gamma power in schizophrenia patients was also reported for auditory steady state stimulation (Light et al., 2006; Spencer et al., 2008). Whatsoever, Gordon et al. (2001) also reported auditory GBR power increases in relation to positive schizophrenia symptoms. Also associations the of gamma phase-locking factor (PLF) with positive schizophrenia symptoms have been reported in auditory paradigms (Spencer et al. 2008; 2009). The PLF is a measure of the degree to which EEG phase is consistent across trials, reflecting event-locked synchronized activity (Spencer et al. 2014). Evidence for increases of gamma connectivity in schizophrenia comes from the auditory dichotic listening paradigm, showing increases of inter-hemisphere gamma connectivity in patients (Mulert et al., 2011). Also, gamma resting-state connectivity was found to be increased in schizophrenia patients (Andreou et al., 2015).

While the role of evoked oscillatory activity in the gamma-band frequency range in schizophrenia is relatively well established, there is much fewer evidence on abnormalities in visual processing. So far, only one earlier EEG study aiming at visual gamma oscillations in schizophrenia reported an association of the visual evoked phase-locking factor (PLF) with positive symptoms in schizophrenia (Spencer et al., 2004). Krishnan et al. (2005) reported a decrease in visual gamma power within a steady state paradigm. One hypothesis regarding the inconsistencies on sensory gamma measures could be conflicting mechanisms operating in top-down versus bottom-up processes of perception and attention, as proposed in the attention model of aberrant salience for fMRI described in paragraph 1.3.3 and 1.4.3.

1.5.4 Gamma oscillations as neurophysiological correlate

At the cellular level of local microcircuits, the occurrence of gamma oscillations is strongly suggested to be induced via fast-spiking interneurons based on excitatory input by pyramidal cells (Bartos et al., 2007; Cardin et al., 2009). Thereby, the initial activation

of the pyramidal cells firing at low theta (1-7 Hz) frequencies (Mann et al., 2005; Fuchs et al., 2007) selectively gets synchronized, establishing activity at fast gamma frequencies (Hasenstaub et al., 2005; Fries et al., 2001). As a result, the synchronization of cell assemblies involved in a task enhances the transmission of higher-frequency activity in the cortex (Engel et al., 2001), as for top-down signal strengthening. Fries et al. (2007) suggest that the gamma cycle converts the excitatory input to a pyramidal cell into a temporal code. The most relevant receptor type for this process is the N-methyl-D-aspartam (NMDA) receptor. Lisman et al. (2008) provide a circuit-based framework model on NMDA hypofunction in relation to fastspiking GABAergic (gamma-amino-butyric-acid) interneurons and glutamatergic pyramidal cells. The NMDA receptor is known to be relevant for schizophrenia, as NMDA receptor antagonists cause temporary exacerbation of schizophrenia symptoms. This mechanism is assumed to reduce excitation of fastspiking interneurons, causing disinhibition of pyramidal cells. Nakazawa et al. (2012) argue in their review that GABAergic, particularly parvalbumin-positive interneurons are disrupted in schizophrenia. It is put forward that these interneurons are crucial for temporal control of cortical inhibition and for the generation of synchronous membrane-potential gamma-band oscillations. Nevertheless, the complex interplay of involved neurotransmitters and receptors in this process and their associated dysfunctions in schizophrenia are not yet sufficiently understood.

1.6 Rationale for the experiments

Considering the research concerning the phenomenon of aberrant salience, as described in the introduction, a gap remains between the approaches in the variety of fields. On the one hand, neurobiological research on the phenomenon mainly aimed at reward-related processes or ambiguous stimulus processing, carried out using fMRI, only (1.4-1.4.3). On the other hand, the crucial role of gamma oscillations in schizophrenia and its multifaceted role in sensory processing never had been aimed at aberrant salience, previously (1.5.1-1.5.3). Especially the perception-prediction approach, as recently reformulated grounding this theory on the neurophysiological basis of a sensory prediction error associated with increased activity of pyramidal cells (Friston et al., 2014) requires experimental evidence.

1.6.1 Scientific goals and objectives

This thesis combines a perceptual perspective on aberrant salience with research on early sensory processes in the gamma frequency, which can be related to underlying neurophysiological processes (1.5.4). As known from the famous 1980's behavioral experiments on pop-out paradigms (Treisman, 1988), physically salient stimuli are automatically selected as behaviorally relevant and may serve as alarming "circuit-breaker" stimuli, putatively activating the DMN, as pointed out in the attention model of aberrant salience (1.3.3 and 1.4.3). The overarching research question of the present thesis is, whether physical salience processed by early sensory gamma mechanisms (1.5.2) could be a sufficient prerequisite for abnormal perceptual experience in participants with positive schizotypal personality traits (study 1) and in patients with schizophrenia suffering from positive symptoms (study 2). As described in the paragraphs 1.1-1.3, the positive symptom of delusion in schizophrenia patients is assumed to be closely related with the phenomenal experience of aberrant salience. In schizotypal personality, aberrant salience is similarly assumed to be related with the positive dimension of schizotypy.

This research question also is derived from inconsistent results on the reward model of aberrant salience, described in paragraph 1.3.2 and 1.4.2. It is pointed to the idea that the shared key aspect of those studies showing an association of positive symptoms with increased activation in the ventral striatum could be an effect of neutral stimuli, which are physically salient (Jensen et al., 2008; Murray et al., 2008; Roiser et al., 2013). Therefore, processing of physical salient stimulus input apart from a reward context is implemented in the two studies of this thesis. Furthermore, unexpectedness and physical salience of an external stimulus, as central to the perception-prediction model of aberrant salience (1.3.1 and 1.4.1) is evident for the evocation of a sensory prediction-error. Based on the hypothesis of a crucial role of physical stimulus salience, such as intense colors in the visual modality, an experimental paradigm for EEG was newly established implementing irregular occurrence of physically salient stimuli (1.7.2). Physically salient stimuli, which are irrelevant for an ongoing target-detection task, are supposed to evoke a sensory prediction error, which was postulated to be associated with superficial pyramidal cells (Friston et al., 2014). Taking on the perspective of sensory selection on aberrant salience, the transfer to the field of gamma oscillations might be fruitful.

1.6.2 Hypotheses study 1: Salience processing and schizotypal personality

Transferring this rationale on early evoked GBR, the following hypotheses were posed for study 1, assessing physical salience processing in healthy participants in relation to schizotypal personality traits:

1a) The early evoked GBR in the visual modality at occipital sites is increased in a condition containing irregularly occurring, physical salient stimuli compared to a non-physically salient condition during an easy target-detection (top-down) task.

1b) Increased power of the early evoked GBR in the visual modality at occipital sites during processing of physically salient sensory input is associated with more positive schizotypal personality traits.

1.6.3 Hypotheses study 2: Salience processing in schizophrenia patients

Subsequent to the first study, the research question was also applied on patients with schizophrenia and schizophrenia spectrum disorder to assess the following hypotheses:

2a) The early evoked GBR in a condition containing irregular occurring, physically salient stimuli in the visual modality, is increased at occipital sites compared to a condition with non-physically salient stimuli during a simple top-down task.

2b) In schizophrenia patients, the early evoked GBR in the visual modality is decreased at occipital sites in a condition containing non-physically salient stimuli within a target-detection task with a top-down attention focus, as compared to matched healthy controls, shown repeatedly for the auditory modality (paragraph 1.5.3; e.g. Leicht et al., 2010).

2c) In schizophrenia patients, the early evoked GBR in the visual modality is increased at occipital sites in a condition containing irregular occurring, physically salient stimuli, as compared to matched healthy control participants.

2d) Aberrant neurophysiological processing of physically salient sensory input is associated with more positive symptoms in schizophrenia and schizophrenia spectrum patients.

2. Material and methods

Following the rationale pointed out above, transfer and assessment of the central hypothesis on aberrant physical salience processing to the research field of gamma oscillations was carried out using EEG.
Both studies comprised an assessment of demographic and psychometric data, as well as measurement of electrophysiological signals during a visual target-detection task implementing irregularly occurring, physical salient stimuli. The central method applied for the analysis of the EEG data is time-frequency analysis of the signal in the gamma-frequency.

2.1 Sample descriptions

Both studies were approved by the local ethics committee of the Medical Association Hamburg. During the whole procedure, the declaration of Helsinki of 1975, as revised in 2008, was incorporated. All participants were informed orally and in written form that their participation is voluntary and that they can refrain from participation at any time during the procedure without any disadvantages. All participants were paid for the time spent on participation (8.50 Euro per hour).

2.1.1 Study 1: Healthy participants

The sample of the first study consisted of initially N = 26 healthy participants, recruited via internet advertisement from Hamburg and the surrounding area. After exclusion of 2 datasets due to substantial contamination by artifacts, a total of N = 24 subjects, (11 men and 13 women) was included for result evaluation. The mean age of this sample was 33.8 years, (SD 11.6). The mean numbers of years spent in education in the sample was M = 16.02 (SD 3.0). All participants were right-handed.
Before the experiment started, a detailed assessment on the medical and neuropsychiatric history of the participants including a short SCID screening (Wittchen et al., 1997) and a toxicology screening was carried out.

Exclusion criteria for participation were:

- Past or ongoing neurological or psychiatric conditions
- Severe somatic conditions
- Drug abuse
- Intake of prescribed medication within 4 weeks preceding the experiment
- Alcohol abuse
- (Un-corrected) vision impairment, e.g. colorblindness
- Left-handedness

Psychometric data was collected on schizotypal personality traits, as individual measure on dimensional schizotypy. The full version of the schizotypal personality questionnaire (SPQ; Raine, 1991) was completed by all participants. The mean score of the sample was M = 15.7 (SD 9.3). Scores varied in the range of 0 – 33, below the cutoff of 41 scores set by Raine (1991) for severe proneness for schizotypal personality disorder. Therefore, the sample can be considered as sub-clinical.

Moreover, the subdivision of schizotypal personality was considered, calculating the positive (cognitive/perceptual), negative (interpersonal) and disorganized subscales (Raine et al., 1994) in analogy to the positive, negative and disorganized symptom dimension in schizophrenia patients. The positive score of the SPQ comprises the four subscales: (1) Ideas of reference, (2) Magical thinking, (3) Unusual perceptual experiences, (4) Paranoid ideation (Suspiciousness). The positive mean score of the sample was M(pos) = 6.92 (SD 4.5).

The negative score of the SPQ comprises the three subscales (5) Social anxiety, (6) No close friends, (7) Constricted affect. The mean score of the negative subscale in the sample was M(neg) = 5.83 (SD 4.6). The disorganized score of the SPQ comprises the two subscales (8) Odd behavior and (9) Odd speech. The mean score of the disorganized subscale of the SPQ in the sample was M(dis) = 2.92 (SD 3.0).

2.1.2 Study 2: Schizophrenia patients and matched healthy controls

The total number of recruited patients for the second study on schizophrenia and schizophrenia spectrum disorders consisted of N = 27 patients with ICD-10 diagnosis of

paranoid schizophrenia (F.20.0) or schizophrenia spectrum disorders (F.25.0; F.23.0). All clinical case participants were recruited from the University Medical Center Hamburg. Diagnoses were confirmed by experienced clinicians of the psychiatric ward and double checked by a senior physician responsible for the discharge papers. Of the N = 27 recruited patients, two datasets had to be excluded due to substantial artifact contamination. Three further datasets had to be excluded due to later detection of neurological complication. Therefore, a total number of N = 22 patients [SZ] could be included into the study. Before participation, a detailed standardized assessment of the personal medical and neuropsychiatric history including a short SCID screening (Wittchen et al., 1997) and a toxicology screening was carried out with all participants.

Exclusion criteria for participation were:

- Past or ongoing neurological or psychiatric conditions
- Severe somatic conditions
- Drug abuse
- Alcohol abuse
- (Un-corrected) vision impairment, e.g. colorblindness
- Left-handedness

Additional exclusion criteria for schizophrenia patients were:

- Suicidal tendency
- Intake of prescribed medication, except antipsychotic and anti-depressant medication of schizophrenia (spectrum) patients
- Intake of Benzodiazepines within 4 weeks preceding the EEG experiment
- Intake of Clozapine (Lorazepam) within 4 weeks preceding the EEG experiment

Of the N = 22 patients, N = 18 were diagnosed with ICD-10 F.20.0 paranoid schizophrenia, N = 3 were diagnosed with ICD-10 F.25.0 schizoaffective disorder and N = 1 patient was diagnosed with ICD-10 F.23.0 acute polymorph psychotic disorder. This heterogeneity of diagnoses was tolerated due to the generizability of the results on the positive psychotic syndrome, which is not only present in paranoid schizophrenia.

Of these patients, N = 13 were first-episode patients, while the other N = 9 patients already had experienced two or more episodes. N = 15 of the patients were male and N = 7 female. The mean age within the patient sample was M = 31.1 (SD 11.5), the mean age at disease onset was M = 26.0 (SD 8.4) and the mean duration of the disease M = 5.2 (SD 7.6). The type of antipsychotic medication varied within patients and was specified by calculating the chlorpromazine equivalence level (CPZ) for all patients (M = 358; SD 312.7). N = 5 patients were unmedicated, N = 6 of the patients received atypical antipsychotic medication only, and N = 10 patients received atypical antipsychotic and antidepressant medication. N = 1 patient received atypical and typical antipsychotic medication. The number of years spent in education within the patient sample was M = 15.8 (SD 4.2).

Accordingly, N = 22 matched healthy control participants [HC] were recruited via internet advertisement from Hamburg and its surrounding area, matching for age (M = 34.1; SD 11.0), sex (15 male; 7 female) and education (number of years spent in education M = 16.3; SD 3.3) to SZ (with no significant mean differences regarding these variables).

All patients were rated by experienced clinicians on the PANSS during the same week the EEG measurement took place. The total PANSS score and five subscales for positive, negative, disorganized, excitement and emotional distress symptoms were obtained. The five-factor model was validated based on a ten-fold cross-validation in a large sample of N = 5769 patients (van der Gaag et al., 2006). The total PANSS score in the patient sample was M = 56.2 (SD 13.4).

The positive subscale comprises the 8 items (1) P1 (delusions), (2) P3 (hallucinations), (3) G9 (Unusual thought content), (4) P6 (Suspiciousness), (5) P5 (Grandiosity), (6) G1 (Somatic concern), (7) G12 (Lack of judgment and insight), (8) G16 (Active social avoidance) and subtracted item N5 (Difficulty in abstraction). The mean positive score in the sample was M = 13.6 (SD 6.3).

The negative subscale comprises the 9 items (1) N6 (Lack of spontaneity), (2) N1 (Blunted affect), (3) N2 (Emotional withdrawal), (4) N4 (Apathetic social withdrawal), (5) G7 (Motor retardation), (6) N3 (Poor rapport), (7), G16 (Active social avoidance), (8) G8 (Uncooperativeness), (9) G13 (Disturbance of volition) subtracted by item P2 (Conceptual disorganization). The mean negative score in the sample was M = 14.1 (SD 5.2).

The emotional distress subscale comprises the 8 items (1) G2 (Anxiety), (2) G6 (Depression), (3) G3 (Guilt), (4) G4 (Tension), (5) P6 (Suspiciousness), (6) G1 (Somatic concern), (7) G15 (Preoccupation) and (8) G16 (Active social avoidance). The mean emotional distress score in the sample was M = 16.2 (SD 4.8).

Tab. 1: *Basic demographic and clinical data of schizophrenia patients (SZ) and matched healthy control participants (HC)*

	Schizophrenia Patients [SZ]	**Matched Controls [HC]**
Sex	15 male; 7 female	15 male; 7 female
Duration of education	M = 15.8 (SD 4.2) [years]	M = 16.3 (SD 3.3) [years]
Age	M = 31.1 (SD 11.5) [years]	M = 34.1 (SD 11.0) [years]
WMS-III-R	M = 9.4 (SD 1.8)	M = 8.7 (SD 2.4)
Age at illness onset	M = 26.0 (SD 8.4) [years]	-
Duration of illness	M = 5.2 (SD 7.6) [years]	-
Diagnosis ICD-10		
Paranoid Schizophrenia: Schizoaffective Disorder: Acute Polymorph Psychotic Disorder:	F20.0: N = 18 (81.8%) F 25.0: N = 3 (13.6%) F 23.0: N = 1 (4.5%)	-
First episode patients	N = 13 (59.1 %)	-
Medication type		
Unmedicated: Atypical only: Atypical & antidepressant: Atypical & typical:	N = 5 (22.7%) N = 6 (27.3%) N = 10 (45.5%) N = 1 (4.5%)	-
Chlorpromazine equivalence (CPZ)	M = 358.0 (SD 312.7) [CPZ]	-
PANSS (total)	M = 56.2 (SD 13.4)	-
PANSS (pos)	M = 13.6 (SD 6.3)	-
PANSS (neg)	M = 14.1 (SD 5.2)	-
PANSS (dis)	M = 18.1 (SD 5.1)	-
PANSS (exc)	M = 12.0 (SD 3.2)	-
PANSS (emo)	M = 16.2 (SD 4.8)	-

The disorganized subscale comprises the ten items (1) N7 (Stereotyped thinking), (2) G11 (Poor attention), (3) G10 (Disorientation), (4) P2 (Conceptual disorganization), (5) N5 (Difficulty in abstraction), (6) G5 (Mannerism), (7) G12 (Lack of judgment and insight), (8) G13 (Disturbance of volition), (9) G15 (Preoccupation), (10) G9 (Unusual thought content). The mean disorganized score in the sample was M = 17.63 (SD 4.9).
The excitement subscale comprises the 8 items (1) G14 (Poor impulse control), (2) P4 (Excitement), (3) P7 (Hostility), (4) G8 (Uncooperativeness), (5) P5 (Grandiosity), (6) N3 (Poor rapport), (7) G4 (Tension), and (8) G16 (Active social avoidance). The mean excitement score in the sample was M = 12.0 (SD 3.2).
Furthermore, the visual working-memory span was assessed in all participants using the WMS-III-R (Wechsler-memory scale - revised; Härting et al., 2000) as a measure for neurocognitive functioning. Demographic, neurocognitive and clinical data of schizophrenia patients and matched healthy control subjects are presented in tab. 1.

2.2 **Setting of the task: The salience paradigm** (study 1 and study 2)

Following the hypothesis regarding physical stimulus salience, a new paradigm applicable for EEG in both, study 1 and study 2, was required. A successful auditory choice-reaction paradigm (Leicht et al., 2010; 2011) was adapted for the visual modality and expanded by a physical salience condition. As the standard target-only (TO) condition (75% of total trials), an equal number of bright grey [RGB 176 176 176] and dark-grey [RGB 86 86 86] target crosses were presented individually at the central position of the screen on a homogenous medium grey background [RGB 126 126 126] (Fig. 9, top-row). The 270 trials of the TO condition were of low physical salience.
Additionally, and in contrast to the auditory paradigm by Leicht et al. (2010; 2011), a second condition was implemented containing intensely colored physically-salient distracter (PSD) stimuli. These stimuli were not relevant for the ongoing target-discrimination task. The distracters were colored discs around the targets: either red [RGB: 225 0 0], green [RGB: 0 255 0] or blue [RGB: 0 0 255] (Fig. 9, bottom-row). These 90 further trials were pseudo-randomly intermixed with the stimuli from the TO condition, resulting in a ratio of 25% PSD trials. Participants were instructed to respond to the target-crosses in both conditions by button-press (left for bright-grey targets, right for dark-grey targets). The total of 360 trials was presented for 250ms per trial at a visual

angle of 4. The inter-stimulus interval (ISI) between trials was varied in the range of 2500–7500ms, during which the grey background was displayed. During pseudo-randomization, direct succession of distracter trials was avoided.

Fig. 9: *The salience paradigm: bright- and dark grey stimuli in the target-only (TO) condition and intensely colored, salient stimuli in the physically-salient-distracter (PSD) condition.*

The trials were separated into four blocks in order to allow for relaxation of the eyes between the blocks. The software used for displaying the paradigm on the screen was Presentation software (Version 15.0, Neurobehavioral Systems). A short test run including instructions was carried out before the beginning of the measurements. The registration of reaction times (RT) was calculated for all correct trials measuring the time from stimulus onset to button press. Behavioral errors were defined as incorrect first button-presses and first button responses later than 1500ms post stimulus onset.

2.3 **Research method: The electroencephalogram (EEG)** (study 1 and study 2)

Electroencephalography is an efficient method of low-risk for the assessment of brain waves with high temporal resolution. The general principle of EEG functioning is described in the introductory paragraph 1.5. The identical paradigm and identical steps of processing were carried out separately for the data obtained in study 1 and the data obtained in study 2.

2.3.1 EEG data acquisition

The recording of the EEG took place at the Psychiatry-Neuroimaging department of the University Medical Center Hamburg in a sound-attenuated, darkened and electrically shielded cabin. Participants were asked to sit down in a slightly reclined chair (if required) with a foot rest and a head rest at a viewing distance of 135 cm in front of a 22'' concurrent-flow monitor (Faytech, Shenzhen, China). The refresh rate of the monitor was 60Hz. EEG activity was recorded continuously using a 64 channel actiCAP system (Brain Products GmbH, Munich, Germany) via Ag/AgCl electrodes.

The electrodes configuration corresponded to an extended 10/20 system with the additional positions: AF7, AF3, AF4, AF8, F5, F1, F2, F6, F10, FT9, FT7, FC3, FC4, FT8, FT10, C5, C1, C2, C6, TP7, CPz, TP8, P5, P1, P2, P6, PO3, POz, PO4.

Four additional electro-oculography (EOG) channels positioned at the outer canthi bilaterally and infra- and supraorbitally on the right were used to record eye movements. The recording of the EEG was carried out using the Brain Vision Recorder software Version 1.10 (Brain Products, Munich, Germany). In order to establish contact between the electrodes and the scalp, SuperVisc electrode gel (EASYCAP GmbH, Herrsching, Germany) was used. The impedances were kept below 5kΩ (10kΩ for the EOG channels). The recorded sampling rate was 1000 samples per second.

2.3.2 EEG data preprocessing

The Brain-Vision Analyzer software (Version 2.02, Brain Products, Munich, Germany) was used for EEG recording. The frequencies below 20 Hz and above 120 Hz were filtered from the data applied with slopes of 24db/oct. During recording, all electrodes were referenced to FCz, while the electrode AFz served as ground electrode. After downsampling to 500Hz, all electrodes were re-referenced digitally to the common average.

In order to remove potential microsaccade artifacts, residual blink artifacts and cranial muscle artifacts from the data, independent component analysis (ICA) was applied following Carl et al. (2012). For the identification of components representing muscle activity, an algorithm based on the power spectrum of each component was applied.

As the relation of power and frequency of EEG and MEG signals approximately follows a 1/f (f stands for frequency) distribution (Buzsaki & Draguhn, 2004), signal power of neural origin declines with the increase of frequency. This is not so for muscle activity. Therefore, the power spectrum of each component was derived from a fast Fourier transform (30–120 Hz; 1 Hz steps) and was correlated (Pearson's coefficient) with the 1/f function, (f = 30, 31, 32,…, 120). All independent components with a power spectrum correlating lower than r = .85 with the 1/f function were considered not to be of neural origin and therefore were rejected. This analysis was carried out exported data using the MATLAB software package (MATLAB 13a, The MathWorks Inc., Natick, MA).

Additionally, independent components reflecting eye or microsaccade topographies and time course were rejected. Thereby, objectivity in the selection of artifactual components was increased, reducing noise in the data. The obtained data can be considered as very clean and of neural origin.

For the cleaned data, trial segments from 300 ms before stimulus onset to 1500 ms after stimulus onset were separated. Further artifact rejection was carried out based on two criteria in the timeframe of 300 ms before stimulus onset to 1000 ms after stimulus onset. The first was a gradient criterion, by which the maximal allowed voltage step was 20μV and the second was an amplitude criterion on ± 20μV within a segment. Segments outlying these criteria were rejected. Then, a baseline correction from 300-100ms pre-stimulus onset was performed.

Due to an expected gamma peat at the frequency at about 40Hz based on the literature for the visual early evoked GBR (Herrmann & Mecklinger, 2001; Senkowki & Herrmann, 2002; Busch et al., 2004; 2006), the data was filtered from 30 to 50 Hz. All trials with a correct behavioral response in the salience condition, as well as the equal number of randomly selected correct trials from the baseline condition were assessed in the further analyses for all subjects.

2.3.3 The early evoked gamma-band response (GBR)

In the visual modality, the early evoked GBR was observed repeatedly in healthy participants during sensory processing at 40Hz about 100ms post-stimulus at occipital electrodes as described in paragraph 1.5.2. For schizophrenia patients, there are only a few studies on evoked power of the early visual GBR, described in paragraph 1.5.3. The

evoked gamma activity in the experimental approach was described with a wavelet transformation [complex Morlet wavelet with the formula Wc (t) = A exp (-t2/2) exp (ict), Morlet parameter c = 3, Gabor normalization], suggested by Herrmann et al. (2005). The method of complex morlet wavelets is a frequently used analysis in order to reveal the phase-locked evoked fraction of the gamma-activity (Mulert et al., 2007; Herrmann et al., 1999; Leicht et al., 2010; 2011).

The wavelet transformation was performed on averaged event-related potentials using the Brain-Vision Analyzer software (Version 2.02, Brain Products) with a layer-wise baseline correction -300 to -100 [ms]. Following previous investigations (e.g. Herrmann & Mecklinger, 2001) all analyzes focused on occipital sites over the visual cortex. Peak analyzes were applied to the 40 Hz layers in both conditions, defined as the highest amplitude value 50–150 ms after stimulus onset of electrode Oz. Latencies and amplitudes were detected automatically via the Brain Vision Analyzer software.

2.4 Statistical analyses

All statistical analyses and comparisons were performed with the SPSS-software package (21.0, IBM, Chicago, Illinois). Testing for the violation of statistical pre-assumptions as well as tests on possible variable inter-correlations are described and discussed separately for both studies, as follows.

2.4.1 Study 1: Statistical analyses (schizotypal personality)

In the first study, an average M = 74.1 (SD 9.5) trials were analyzed for each of the two conditions. The statistical pre-assumption of normal distribution of the variables in the result paragraph was not violated by any variable as confirmed by one-sample Kolmogorov–Smirnoff tests. Accordingly, the correlations of GBR-peaks with SPQ scores and subscale scores were calculated two-sided by Pearson's correlation coefficient.

A Bonferroni correction for the multiple calculations of Pearson's correlations with the GBR power peaks was applied. The initially obtained p-values were multiplied by 8 (2 conditions x 4 SPQ measures). This is a very conservative procedure, as (1) our hypothesis towards positive schizotypy was directional and (2) multiple testing of the TO

and PSD peak correlation measures could also be corrected for separately, which would result in a multiplication by 4 (4 SPQ measures per variable).

There were no significant correlations of age with any of the GBR values (TO or PSD), neither with any of the SPQ scores. Also the number of years spent in education was not correlated significantly with any of the GBR values (TO or PSD), neither with any behavioral responses, nor with any of the SPQ scores.

Behavioral results were not significantly correlated with neither of the SPQ scores, nor with any of the GBR values (TO or PSD). Reaction times in the PSD condition ($r = .464$; $p = .022$) but not in the TO condition ($r = .305$; $p = .147$) correlated significantly with the age of participants. Older age was positively correlated with longer reaction times. This incidental finding can be regarded as a normal link with no further implications to the results of the study.

2.4.2 Study 2: Statistical analyses (schizophrenia patients)

In the second study, an average of $M = 59.3$ (SD 17.2) trials was analyzed for each of the two conditions in the schizophrenia patient sample. In the matched healthy control group an average of $M = 66.1$ (SD 17.4) trials was analyzed. The number of trials did not differ significantly between the two groups ($t = 1.315$; $p = .196$).

The statistical pre-assumption of normal distribution for all tested variables was not violated as tested by one-sample Kolmogorov-Smirnoff tests.

Two-way repeated measures ANOVA's (2 conditions x 2 groups), were calculated on the behavioral reaction-times and behavioral error-rates, as well as on the GBR power results. Additional paired t-tests (one-sided) were calculated for the directional hypothesis on GBR power. Correlations of the GBR-peaks in both conditions with the PANSS and its subscores were calculated two-sided by Pearson's correlation coefficient. A Bonferroni correction was applied afterwards, (p-values were multiplied by 12) in order assess the results with regard to multiple testing. This is a very conservative procedure, as (1) our hypothesis towards positive schizophrenia symptoms was directional and (2) multiple testing of the TO and PSD peak correlation measures could also be corrected for separately, by a multiplication of the obtained p-values by 6.

The additional exploratory calculation of correlations of the GBR-peaks in the physically-salient distracter condition with the single PANSS items were calculated with

Spearman's correlation coefficient (two-sided), as the single-items on a 1 to 7 scale cannot be considered normally distributed. This exploratory analysis was not p-value corrected. There were no significant correlations of age, education or chlorpromazine equivalence dosage (CPZ) with any of the PANSS scores, nor with evoked power in any of the conditions, with two exceptions. (1) There was a significant negative correlation of the CPZ with the positive subscale of the PANSS ($r = -.474$; $p = .026$), showing that a higher dosage of antipsychotic medication in the patient sample was correlated with less positive symptoms, with no further implications to the results of the study. A second exception was a significant positive correlation of age in the patient sample with evoked power in the PSD condition ($r = .622$; $p = .001$), this association was not present in the matched healthy controls ($r = .037$; $p = .871$) and presumably reflects progression of disease in older patients. Therefore, separate analyses on the subgroups of first-episode patients vs. chronic patients, was additionally assessed in the results paragraph. Duration of disease in the patient sample was significantly correlated with the PANSS positive score ($r = .576$; $df = 21$; $p = .005$) and with the GBR power in the PSD condition ($r = .662$; $df = 21$; $p = .001$).

Behavioral reaction times were also correlated with age in the schizophrenia patient sample in both, the TO ($r = .470$; $p = .027$) and in the PSD ($r = .570$; $p = .006$) condition. In the matched healthy control participants this association was a trend for the PSD condition ($r = .411$; $p = .057$) and not present in the TO condition ($r = .327$; $p = .138$).

These associations can be seen as a normal link of older age and longer reaction times with no further implications to the results of the study, as reaction times were not significantly correlated with any further variables from the results paragraph. Nevertheless, controlling for a potential influence of age on the results, the main correlation analysis was additionally calculated by partial correlations, controlling for the variable of age. Significance in the results paragraph is indicated by * for a p-values $< .05$ and by ** for p-values $< .01$.

3. Results

The results obtained from the two studies revealed several links on the topic of aberrant neurophysiological processing of salient vs. non-salient visual stimuli in healthy participants, as well as in patients with schizophrenia. The first study assessed neurophysiological processing of physically salient distracters in healthy participants in relation to schizotypal personality traits, while the second study was carried out on schizophrenia patients and matched healthy controls.

3.1 Study 1: Schizotypal personality traits

In study one the hypotheses were tested within a healthy sample in relation to the dimension of schizotypal personality traits. Schizotypal personality traits are qualitatively less severe than schizophrenia symptoms and enable identification of abnormal neural processes, presumably of relevance for schizophrenia (paragraph 1.2).

3.1.1 Study 1: Behavioral results

Analyzes on the behavioral data were carried on reaction times (RT), measured from the occurrence of a stimulus to the first correct button-press. Individual error rates (ER) were calculated as percentage of trials without correct response within 1500 ms after stimulus occurrence. Within the group of N = 24 healthy participants the analysis of both, RT and ER showed an effect of distraction in the PSD condition as compared to the TO condition.

The mean RT in the PSD condition (599ms; SEM 19.6) was significantly longer than in the TO condition (527ms, SEM 17.7; $t = 9.670$; $p < 0.001$). Also, the mean percentage of errors was significantly higher in the PSD condition (6.9%; SEM 1.2) in comparison to the TO condition (2.7%: SEM: 0.4; $t = 4.087$; $p < 0.001$). The behavioral results, on the reaction-times and the error-rates are displayed separately for the target-only and physically-salient distracter condition in fig. 10.

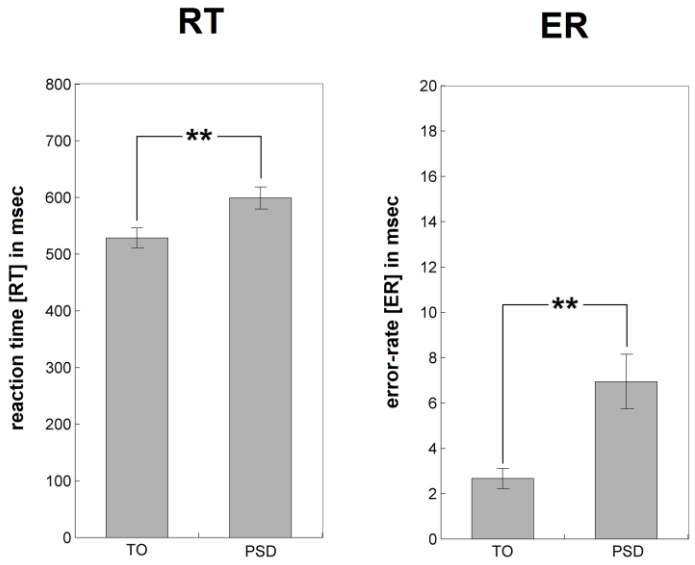

Fig. 10: *Mean reaction times (RT) and error-rates (ER) in healthy participants in the target-only (TO) and in the physically-salient-distracter condition (PSD).*

3.1.2 Study 1: Neurophysiology - The early evoked GBR

Within the group of N = 24 healthy participants the typical GBR peak at 100ms after stimulus onset at 40Hz was observed. Evoked power at electrode Oz was significantly higher in the PSD condition (.0214 μV^2; SD .021*) as compared to the TO condition (.0131 μV^2; SD .019; t = 2.801; p = .037*). The time-frequency diagrams for the visual evoked GBR power are displayed for both conditions in fig. 11.

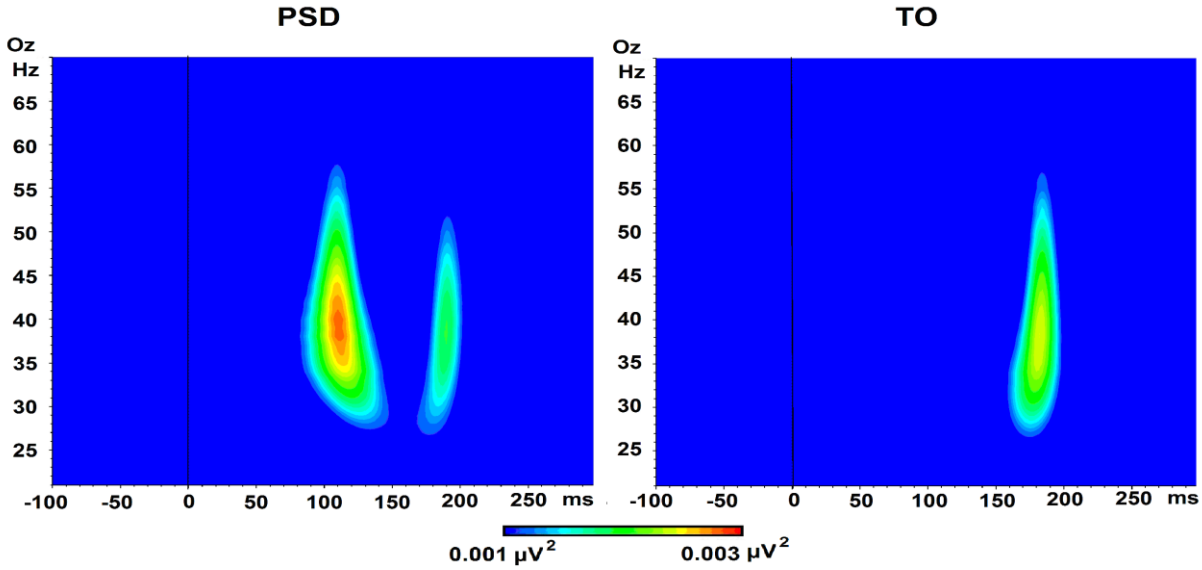

Fig. 11: *Visual evoked gamma-band response (GBR) in healthy participants at 40Hz in the physically-salient-distracter (PSD) and target-only (TO) condition.*

The early evoked GBR power is also displayed for the 40Hz power layer of both conditions and as current-source density (CSD) map for the time period of 50-150ms in the PSD condition in fig. 12. Pronounced activation at occipital sites is present in the PSD condition during this early time-window.

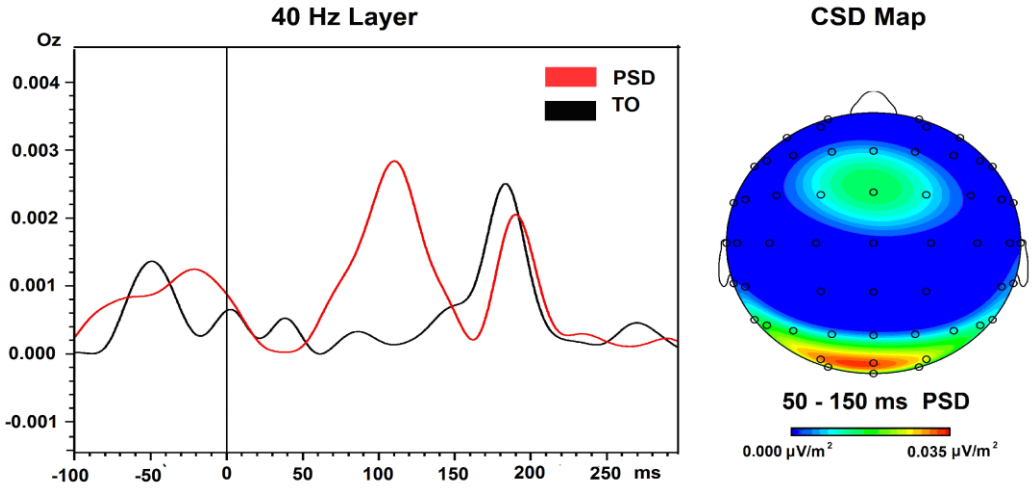

Fig. 12: *Visual evoked gamma-band response (GBR) in healthy participants at 40Hz in the physically-salient-distracter (PSD) and in the target-only (TO) condition as layer (left) and in current source density (CSD) head view (right).*

3.1.3 Study 1: Association with schizotypal personality traits

Within the N = 24 healthy subjects of the first study, a significant correlation of the early visual GBR and the positive dimension of the Schizotypal Personality Questionnaire (Raine, 1991) was revealed in the physically-salient distracter (PSD) condition (r = .588, p = .0.024*). None of the further dimensions (negative or disorganized), nor the total SPQ score were significantly correlated with the 40Hz GBR, neither in the PSD condition, nor in the TO condition. The results of the correlation analysis are displayed in tab. 2. The reported p-values are Bonferroni corrected.

Tab. 2: *Correlations of the evoked gamma-band response (GBR) in the physically-salient-distracter (PSD) condition with the schizotypal personality questionnaire (SPQ) and its positive, negative and disorganized subscales.*

N = 24	**SPQ total**	**SPQ pos**	**SPQ neg**	**SPQ dis**
PSD 40Hz Power				
Pearson correlation	0.356	**0.588***	0.144	0.056
Sig. (2-tailed)	0.704	**0.024**	4.008	6.352
TO 40Hz Power				
Pearson correlation	0.125	0.350	0.059	-0.122
Sig (2-tailed)	4.488	0.672	6.288	4.568
*** Pearson's r, two-tailed significance level p < 0.05, Bonferroni corrected**				

3.2 Study 2: Schizophrenia patients

The second study was carried out in a clinical sample of schizophrenia and schizophrenia spectrum patients. For this study, the relevance of physical salience processing for the clinical context was assessed in relation to the symptom dimensions of schizophrenia. According to the proposition by Os (2009) the saliency syndrome could provide a scientifically grounded approach on psychotic syndromes, cutting across the current diagnostic classification system. As an additional analysis, the subgroup comparison of first-episode patients and patients who experienced more than one episode ("chronic patients") was included into the results evaluation.

3.2.1 Study 2: Behavioral results

Within the group of N = 22 schizophrenia patients (SZ) and N = 22 matched healthy control participants (HC), reaction times (RT) were significantly increased across groups in the PSD condition (M[SZ] = 644ms (SEM 23.3); M[HC] = 614ms (SEM 23.5)) as compared to the mean RT in the TO condition (M[SZ] = 565ms (SEM 17.3); M[HC] = 529ms (SEM 17.7) indicated by a two-way repeated measures ANOVA ($F(1,42) = 133.5$, $p < .0001$**, fig. 13, A). There was no significant effect of group on RT ($F(1,42) = 1.3$ p

= .252). The interaction of condition and group was not significant (F(1,42) = .126, p = .724).

Error-rates (ER) were significantly increased in the PSD condition across groups (M[SZ] = 11.4% (SEM 2.3); M[HC] = 5.9% (SEM 1.1)) in comparison to the TO condition (M[SZ] = 4.9% (SEM 1.1); M[HC] = 2.3% (SEM 0.5)), indicated by a two-way repeated measures ANOVA (F(1,42) = 37.0, p < .0001, fig. 13, B). The mean ER across conditions was significantly higher in the SZ group as compared to the HC group (F(1,42) = 5.2, p = .028*). The interaction of group and condition was a trend (F(1,42) = 2.9, p = .094).

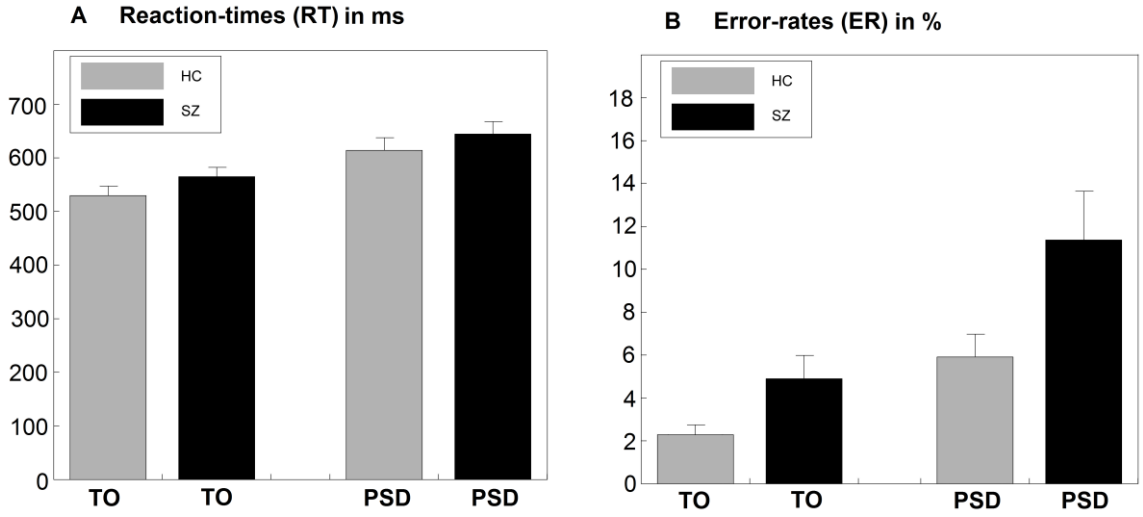

Fig. 13: *Reaction time (RT) and error-rate (ER) in schizophrenia patients and matched controls, target-only (TO) and physically-salient-distracter (PSD) condition*

3.2.2 Study 2: Neurophysiology - The early evoked GBR

Within the group of the N = 22 schizophrenia patients and the N = 22 matched healthy control participants, the following results were obtained for the time-frequency analysis of evoked gamma power at electrode Oz. Evoked power at the frequency of 40Hz was significantly increased across groups in the physically salient distracter (PSD) condition (M[SZ] = .0264 (SD .019); M[HC] = .0169 (SD .012)) in comparison to the target-only (TO) condition (M[SZ] = .0100 (SD .011); M[HC] = .0148 (SD .010)), as revealed by a two-way repeated measures ANOVA (F(1,42) = 15.0; p < .0001**). The diagram of

means is displayed in fig. 14, A. Furthermore, there was a significant interaction of group and condition (F(1,42) = 9.0; p = .005**), while there was no significant effect of group across conditions (F(1,42) = .520; p = .475). The current source density (CSD) whole-head topographies for both groups in the PSD condition are displayed in figure 14, B for the time-window of the evoked GBR.

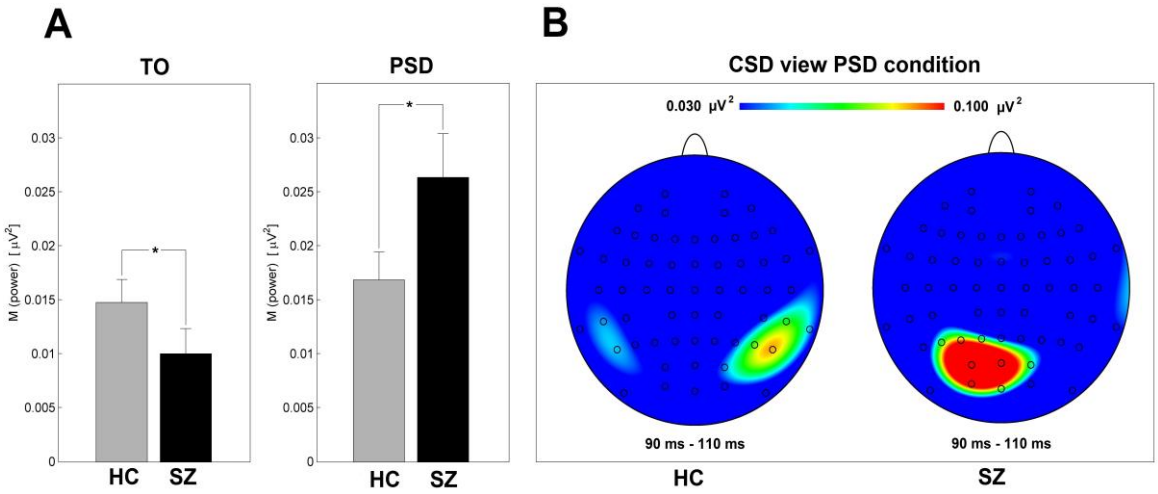

Fig. 14: *(A) Mean visual evoked gamma-band response in the target-only (TO) and in the physically-salient-distracter (PSD) condition for the schizophrenia patient group (SZ) and the matched healthy control group (HC). (B) Current source density (CSD) head views in the PSD condition for HC and SZ (right).*

GBR power in the PSD condition was significantly increased in schizophrenia patients, as compared to matched healthy controls (t = 1.777; df = 21; p = .045*).

In contrast, GBR power in the TO condition was significantly decreased in schizophrenia patients, as compared to matched healthy controls (t = -1.763; df = 21; p = .046*).

Within the schizophrenia patient group, GBR power was significantly increased in the physically-salient distracter condition, as compared to the target-only condition (t = 4.052; df = 21; p = 0.001**). Within the matched healthy control group, GBR power was not significantly increased in the physically-salient distracter condition, as compared to the target-only condition (t = 0.822; df = 21; p = 0.211).

The comparison of first episode patients vs. chronic patients showed a significantly increased GBR in the PSD condition (M(first-episode) = .0174 (SD = .01); M(chronic) = .0394 (SD = .02); t = 3.228; p = .004**) and no significant difference of the GBR in the TO condition for these subgroups (M(first-episode) = .0103 (SD .01); M(chronic) = .0102 (SD .01); t = -.018 ; p = .986).

3.2.3 Study 2: Association with schizophrenia symptoms

Next, the visual evoked 40Hz GBR was assessed in order to test for associations with schizophrenia symptoms, especially for an association of evoked GBR power in the PSD condition and positive schizophrenia symptoms, according to hypothesis (3). Therefore, the evoked GBR in both conditions was correlated with the five subscales of (1) positive, (2) negative, (3) disorganized, (4) excitement and (5) emotional distress symptoms derived for the Positive and Negative Syndrome Scale (PANSS; van der Gaag, 2006) .The results are presented in tab.3.

Tab. 3: *Correlation of the PANSS and subscales in schizophrenia patients, with the GBR in physically-salient-distracter (PSD) and target-only (TO) condition.*

N = 22	***PANSS total***	***PANSS pos***	***PANSS neg***	***PANSS exc***	***PANSS dis***	***PANSS emo***
PSD 40Hz Power						
Pearson correlation	0.523*	**0.738****	0.055	0.105	**0.690****	0.224
Sig. (2-tailed)	0.012	**0.0001**	0.807	0.642	**0.0001**	0.316
TO 40Hz Power						
Pearson correlation	0.066	0.134	0.121	-0.085	0.128	-0.071
Sig (2-tailed)	0.769	0.553	0.593	0.708	0.570	0.752

* Pearson's r (two-tailed): $p < 0.05$;

**** Pearson's r (two-tailed): $p < 0.01$ (sig. after Bonferroni correction)**

The additional analysis of the identical variables was also assessed applying a partial correlation controlling for the variable of age. The results obtained are similar as without controlling for age, presented in tab 4.

Tab. 3: *Partial-correlation of the PANSS and subscales in schizophrenia patients, with the GBR in physically-salient-distracter (PSD) and target-only (TO) condition, controlling for the variable of age.*

N = 22	***PANSS total***	***PANSS pos***	***PANSS neg***	***PANSS exc***	***PANSS dis***	***PANSS emo***
PSD 40Hz Power						
Pearson correlation	0.501*	**0.716****	0.159	0.058	0.617**	0.237
Sig. (2-tailed)	0.021	**0.0001**	0.492	0.804	0.003	0.301
TO 40Hz Power						
Pearson correlation	0.039	0.098	0.134	-0.097	0.088	-0.081
Sig (2-tailed)	0.866	0.671	0.564	0.676	0.704	0.729
* Pearson's r (two-tailed) partial correlation: $p < 0.05$; **** Pearson's r (two-tailed) partial correlation: $p < 0.01$ (sig. after Bonferroni correction)**						

The GBR in the PSD condition was strongly correlated with positive symptoms in the schizophrenia patient group (r = .738, p < .0001**, 95% CI = .460-.884). The correlation plot is displayed in fig. 15.

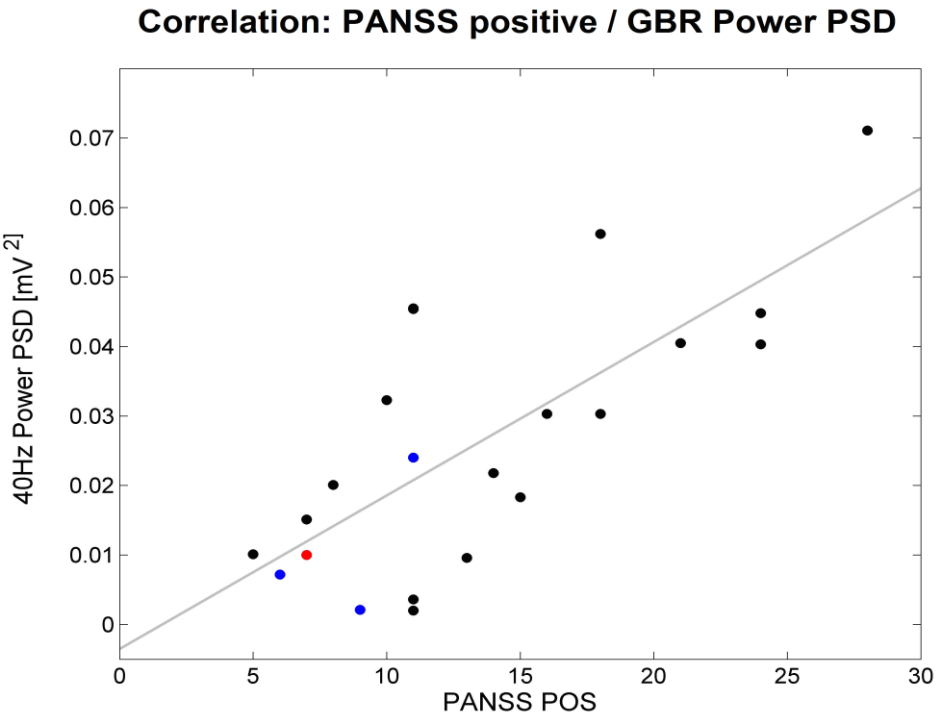

Fig. 15: *Correlation of the 40Hz GBR in the PSD condition with positive PANSS score of schizophrenia symptoms (r = .738; p < .0001**). Black dots correspond to patients with paranoid schizophrenia (F20.0). Blue dots correspond to data of patients with schizoaffective disorder (F25.0). The red dot corresponds to data of a patient diagnosed with acute polymorph psychotic disorder (F23.0).*

Also the disorganized PANSS subscale was significantly correlated with the GBR in the PSD condition (r = .690, p < .0001**; 95% CI = .379-.861). These two results remain significant after Bonferroni correction.

In addition, the question of a relation of the 40Hz GBR in the PSD condition with specific symptomatic aspects obtained by the single items of the PANSS was explored. Spearman's correlations (φ) for the 30 PANSS items with GBR power in the PSD condition were calculated. (This non-parametric measure was preferred in this case, as the single item scale of the PANSS only varies within the range of 1 to 7 scores). The result is presented in tab 4. Items referring to delusional thought content (G9: unusual thought content; P1: delusions; P5: grandiosity, P6: suspiciousness/persecution) were correlated with the GBR in the PSD condition. Also item G12: lack of judgment and insight, suggesting more severe affliction by delusion, was significantly correlated with the GBR power in the PSD condition. These exploratory results are not Bonferroni corrected.

Tab. 4: *Spearman's correlations of the 40Hz GBR in the physically-salient-distracter (PSD) condition with the PANSS items. Dark grey items correlate significantly (uncorrected two-tailed; p < 0.001); brighter grey item obtained a correlation coefficient φ > .3.*

PANSS item	Spearman's rho	p-value
1. Unusual thought content (G9)	**φ = .712****	**p < .0001**
2. Lack of judgment and insight (G12)	**φ = .622****	**p = .003**
3. Grandiosity (P5)	**Φ = .513***	**p = .017**
4. Delusions (P1)	**φ = .492***	**p = .023**
5. Suspiciousness/Persecution (P6)	φ = .421	p = .057
6. Active social avoidance (G16)	φ = .398	p = .074
7. Preoccupation (G15)	φ = .377	p = .092
8. Stereotyped thinking (N7)	φ = .369	p = .099
9. Conceptual disorganization (P2)	φ = .365	p = .104
10. Poor attention (G11)	φ = .331	p = .142
11. Hostility (P7)	φ = .306	p = .177
12. Passive/apathetic social withdrawal (N4)	φ = .301	p = .185
13. Poor impulse control (G14)	φ = .298	p = .189
14. Disturbance of volition (G13)	φ = .261	p = .254
15. Emotional withdrawal (N2)	φ = .233	p = .310
16. Difficulty in abstract thinking (N5)	φ = .230	p = .316
17. Somatic concern (G1)	φ = .180	p = .436
18. Hallucinatory behavior (P3)	φ = .156	p = .498

19. Tension (G4)	φ = .044	p = .849
20. Depression (G6)	φ = .032	p = .890
21. Poor rapport (N3)	φ = .022	p = .923
22. Guilt feelings (G3)	φ = .008	p = .972
23. Lack of spontaneity and flow of conversation (N6)	φ = -.027	p = .907
24. Excitement (P4)	φ = -.068	p = .770
25. Uncooperativeness (G8)	φ = -.080	p = .729
26. Mannerisms and posturing (G5)	φ = -.087	p = .707
27. Disorientation (G10)	φ = -.089	p = .703
28. Anxiety (G2)	φ = -.135	p = .559
29. Motor Retardation (G7)	φ = -.188	p = .611
30. Blunted affect (N1)	φ = -.360	p = .109

** bold values indicate uncorrected two-tailed significance Spearman ($p < 0.001$)
* bold values indicate uncorrected two-tailed significance Spearman ($p < 0.005$)

3.2.4 Contents of aberrant salience

In addition to the experimental approach, all participants from study 2 (schizophrenia patients and matched healthy controls) were asked based on a non-validated exploratory questionnaire for the occurrence of aberrant salience during their course of the illness. N = 19 of the N = 22 patients (86.4%) confirmed to have experienced aberrant salience for an episode during their illness, answering at least one of the following questions with yes. Only N = 3 of the N = 22 patients (13.6%) denied to ever have experienced aberrant salience.

1. Going through the streets, it happens that there are specific symbols or words with a personal message for me.
2. Sometimes I get the impression that there are references in the surrounding showing me what to do.
3. From time to time I see or read something on posters or other things, which is directly linked to my current situation.
4. Some combinations of letters occurring to me contain hidden messages.
5. Every now and then, the newspaper headlines make hints to my life.

N = 12 of the N = 22 schizophrenia patients (54.5%) agreed to specify the topics of their subjective contents of aberrant salience. The topics mentioned are listed here, to a large part referring to typical content of delusions (described in paragraph 1.3):

- “Family”
- “Love”
- “Religion” (“Judaism”, “Christianity”, “biblical motives”, “messages from god”, “sheep and guilt”)
- “Illuminati”
- “Existence”
- “The Self” (“encouragement to fight”, “humiliation if fight is neglected”)
- “Persecution”
- “Eyes”
- “Drugs” (“Cannabis”)
- “Life” (“attitude towards life”, “plan for life”, “path of life”, “turning back”)
- “Politics” (“political conviction”)
- “Apocalypse”
- “Order to act (buy)”
- “Decay”
- “Fear”
- “The meaning of numbers” (“zero / 0”)
- “Formation of pairs”
- “Work situation”
- “Name of the father’s dog“
- “The contents correspond to the voices” (auditory hallucinations)

Interestingly, also N = 6 of the N = 22 healthy control participants (27.3%) answered at least one of the questions with yes. However, the topics mentioned appear less distressing.

- “Profession”
- “Economy” (“employment market”, “stock exchange”)
- “Relationships” (“family”, “partnership”)
- “Advertising” (“for cars”, “for habitation”, “for food if hungry”)
- “Cooking”
- „Insurance“
- “Ethics”
- “Religion”

4. Discussion

The present thesis contributes to the field of aberrant salience by relating early sensory processing in the gamma frequency to positive schizotypal personality traits and positive schizophrenia symptoms. The experimental results, their classification with regard to the theoretical context of aberrant salience and prospects on possible applications are discussed in the following paragraphs.

4.1 Discussion of the experimental results

Behavioral results show increased error-rates and reaction-times in the PSD condition, as compared to the TO condition in healthy participants in study 1 and across groups for study 2, demonstrating an effect of behavioral distraction by physically salient stimuli. A significantly increased error-rate across conditions for schizophrenia patients in comparison to matched healthy control participants replicates behavioral results from an auditory choice-reaction task by Leicht et al. (2010), while reaction-times in the schizophrenia sample were not significantly increased. These relatively normal reaction times in the patient sample are in line with the well preserved cognitive capacity in the patient sample, assessed by the visual working-memory span (WMS-III-R), which also did not differ significantly between patient sample and the matched healthy control group (paragraph 2.1.2).

Results concerning the early evoked GBR showed increased gamma oscillations during processing of physical salience in a sample of healthy participants in study 1, confirming hypothesis 1a, as well as across groups in study 2, confirming hypotheses 2a. This hypothesis was also confirmed separately within the schizophrenia patient group, while the increase of the GBR was not significant in the matched control group, separately.

Within schizophrenia patients, the subgroup of chronic patients showed increased GBR power in the PSD condition in comparison to first-episode patients. This was not so in the TO condition. Seemingly, this could indicate higher susceptibility for this neurophysiological measure in chronic patients, though this subgroup comparison based on groups of N = 13 and N = 9 should be interpreted cautiously.

In accordance with hypothesis 2b, as well as in accordance with earlier results in schizophrenia on the auditory evoked GBR in settings in need for executive attention (Chen et al. 2014; Leicht et al. 2010; 2011), GBR power in schizophrenia patients was

decreased in the TO condition in comparison to matched healthy control participants. This finding is very well in line with previous research showing difficulties of executive attention in patients with schizophrenia.

Importantly, also hypothesis 2c was confirmed as GBR power was found to be elevated in schizophrenia patients during processing of physically salient distracter stimuli in the PSD condition. This finding is interesting as excesses of neural parameters are less likely to be a side-effect of generally reduced cognitive ability or dampening by psychopharmacological effects. The differential effects between the two conditions in schizophrenia patients and matched healthy controls are reflected in the significant interaction of group (SZ vs. HC) and condition (TO vs. PSD) in study 2 on the schizophrenia patients and are confirmed by the significant t-tests calculated separately for the TO and PSD conditions.

Distinguishing differential effects of effortful processing versus processing of unexpected salience, as also referred to in the attention network model of aberrant salience (paragraph 1.3.3 and 1.4.3), might be also relevant for an improved understanding of abnormal gamma activity and neurocognitive disturbances in schizophrenia, with regard to symptom formation. The present finding suggests an important role of physical stimulus characteristics in neuronal transmission, putatively relating to impaired cortical inhibition of salient distracters. Correspondingly, Yoon et al. (2010) showed that a GABA deficit in visual cortical areas leads to impaired cortical inhibition in subjects with schizophrenia in the case of orientation-specific surround suppression.

Moreover, increases of GBR power in the condition containing a physically salient distracter were significantly correlated with questionnaire-identified positive trait schizotypy in healthy participants confirming hypothesis 1b, as well as with more severe positive symptoms in the schizophrenia patient group, confirming hypothesis 2d. This finding suggests that individuals with higher scores of positive schizotypal personality traits and schizophrenia patients with more severe positive symptoms tend to exhibit a more pronounced evoked GBR towards physically salient visual stimuli with irregular occurrence.

The exploratory analysis of the evoked GBR in the PSD condition with the single PANSS items in the schizophrenia patients was strongest for the items “G9: unusual thought content”, “G12: lack of judgment and insight”, “P5: grandiosity”, “P1: delusions”, and “P6: suspiciousness/persecution”. Following the German standard

classification system for psychopathology (AMDP; 2007 paragraph 1.2), delusion of persecution and grandiose delusions are listed among delusional contents, while "unusual thought content" and "lack of judgement and insight" can be regarded as indirectly linked with delusional severity by distance from reality. In spite of, this interpretation is not mandatory. This finding relates to results from Roiser et al. (2013) for a sample at ultra-high-risk of psychosis. Roiser et al. (2013) report an association of delusion-like symptoms with the BOLD response in the ventral striatum, obtained with fMRI in a reward paradigm, while the results from this thesis show a similar association of positive schizophrenia symptoms with early sensory processing of physically-salient distracter stimuli in the gamma frequency band, apart from a context of reward.

The results from this thesis suggest neurophysiological processing of physical aberrant salience as a putative neurophysiological marker for the salience syndrome in schizophrenia. This finding relates to several lines of clinical and neurobiological research, described in the introductory paragraphs. The findings provide further (non-causal) empirical support for Nelson et al. (2014) suggesting that neurocognitive disturbances of attention and memory may lead to distorted interpretations of events. In their account it is put forward that e.g. cognitive associations between irrelevant stimuli putatively contribute to delusional thinking, exerting a bottom-up influence on cognitive processes of "meaning-making" in schizophrenia. The findings from this thesis add to this view by including a further mechanism relating to the role of gamma oscillations in early stimulus processing.

Even though a causal link between aberrant processing to delusional ideation cannot be shown by the current results, the strong correlation of the evoked GBR in the PSD condition with both, positive schizotypy and positive schizophrenia symptoms, is compatible with this interpretation.

4.2 Discussion concerning the three models of aberrant salience

The present findings relate to existing theoretical models of aberrant salience described in the paragraphs 1.3.1 - 1.4.3. In order to relate the present results to these existing approaches, the findings are discussed separately with respect to the three models on aberrant salience in the following paragraph.

Initially, the aspect of a physically salient distracter is addressed in the attention-model of aberrant salience (paragraphs 1.3.3 and 1.4.3). Even though the attention-model

focuses on brain networks as assessed with fMRI, the idea of an external stimulus capturing attention within the DMN network is very much in line with the results from the current thesis on an early sensory processing level assessed with EEG. Even though, the present results of course cannot provide direct evidence for the DMN/CEN network regions in the brain proposed in the attention-model. Importantly, there is no previous experimental evidence on the attention-model of aberrant salience assessing activation by physically salient stimuli in patients with schizophrenia.

Secondly, with regard to the famous account on aberrant salience by Kapur (2003, 2005), the reward model (paragraphs 1.3.2 and 1.4.2), physical stimulus salience is not addressed in this theory, but may be a relevant variable possibly also explaining previous experimental results. As pointed out above, major studies in relation to positive symptoms in the reward system applied physically salient, neutral stimuli within a context of reward (and punishment). As shown by Zink et al. (2006), also salient stimuli without a context of reward are associated with activity in the ventral striatum. The rationale for the present account was to assess the aspect of physical salience apart from a reward setting and in relation with gamma oscillations in sensory processing, which was successful.

Thirdly, also the perception-prediction model of aberrant salience (paragraphs 1.3.1 and 1.4.1) provides interesting theoretical explanations to this field, while experimental evidence is sparse. A recent account on general brain functioning by Friston et al. (2014) refers to this theory postulating a major role of a pathophysiology at the synaptic level in the generation of false beliefs and how they may arise. Therein, the brain is suggested to function as a generator of hypothesis based on internal statistical inference, which are creations of mental images by the brain ("phantasies"), tested against sensory evidence, resulting in a prediction-error (see also Clark, (2013)). The central idea is, that thought content and perceptual prediction-error establish a recursive loop, possibly reinforcing each other in schizophrenia, in the sense that abnormal perception furnishes abnormal thought content and vice versa. The salience paradigm catches this perspective as increased neurophysiological transmission of irregular occurring, physically salient sensory input, provoking a prediction-error on the sensory level is assessed and correlated with positive schizotypal personality traits and positive schizophrenia symptoms being characterized by abnormal perception and abnormal thought content (though a causal link on delusional ideation cannot be confirmed). The perception-prediction theory as such, also suggests that also other forms of salience, as endogenous

salience of personal or generic emotional content (paragraph 1.1), could be projections of internal meaning as top-down influence of subjective thought content on perceived salient sensory input.

A critique on this approach could concern an overlap of aspects from the attention model and the perception-prediction model. Anyhow, these three approaches can be regarded as complementary views on the same phenomenon, highlighting disparate, but connected layers of explanation. The goal in the approach of this thesis was a separation from the reward-context and the transfer to research on early sensory visual processing as measured with EEG, proposing another layer of explanation, relating to all three of the models. A second critique regarding the paradigm could be the concern that the PSD condition is not a pure bottom-up condition. Whatsoever, the behavioral results suggest an effect of distraction in the PSD condition and the only physical difference between the conditions is the salient stimulus. Also it is to state that all paradigms (even under passive viewing conditions) inevitably require at least small amounts of top-down attention by participants.

4.3 Discussion of prospects and applications

With regard to applicability of the experimental findings, this paragraph discusses possible applications and prospects, in which the current results may help to improve treatment of schizophrenia in brain stimulation and psychotherapy.

Recent developments in the application of noninvasive electrical brain stimulation could become more applicable in the future for treating perceptual-neurocognitive deficits. The external application of transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) have already been applied successfully influencing cortical excitability, activity (Schutter, 2014) and conscious experience (Strüber et al., 2014). A review on the available evidence of brain stimulation in schizophrenia by Hasan et al. (2013) gives an overview on first results, concluding that the underlying neurobiology is not yet understood well enough. Weaknesses in the application of these methods remain to be resolved e.g. regarding the power of endogenous brain oscillations interacting with the stimulation (Neuling et al., 2013). More specific results on normal and aberrant conditions of processing in schizophrenia, as assessed in this thesis, are required to further adjust more specific approaches of treatment with brain stimulation.

Another important route for adequately treating patients suffering from schizophrenia is effective and specific intervention in psychotherapy and psychoeducation. Increasing knowledge on the neurocognitive mechanisms and symptomatic outcomes, as obtained by the present results, can help understanding symptom formation and the experience of patients, improving treatment strategies.

The application of knowledge on aberrant stimulus processing to approaches from cognitive-behavioral therapy, as the SORC model (1.2.1), enables the analysis of dysfunctional regulatory circuits of behavior, starting with a stimulus. The micro-processes of perception-based conclusions and cascades of thought related to abnormal salience perception could be dissected and discussed using the knowledge on the emergence of perceptual impressions. The process of embedding a percept into a (subjective) framework of meaning could be target of psychoeducation and cognitive psychotherapy, e.g. as an aspect of meta-cognitive training (MCT) for schizophrenia (Moritz et al., 2014).

Other approaches could aim at subjective contents of aberrant salience (5.1), building on the neuroscientific view of the brain as a generator of hypothesis based on internal statistical inference (phantasies), which are tested against sensory evidence (Friston et al., 2014). Both, the content of perception, as assessed in the questionnaire on subjective aberrant salience could be attempted to get traced back to emotional experiences, trying to understand and resolve conflicts within their psychic origin based on schema therapy approaches (Roediger, 2011). Also projective methods could be an option to work on the delusion related, psychic contents of aberrant salience.

5. Compendium

5.1 English

Background: Within the recent discussion on evidence-based psychiatric classifications, the salience syndrome has been proposed as a key syndrome of schizophrenia (Os, 2009). In the present thesis, aberrant salience (Kapur 2003, 2005) is integrated within the context of clinical as well as neuroscientific approaches on the phenomenon. Further, a new scientific objective regarding the neurophysiology of physical salience perception in the gamma frequency range is derived and implemented experimentally.

Methods: The visual evoked gamma-band response (GBR) at 40 Hz was assessed within two studies in a newly established EEG visual target-detection paradigm. The GBR was calculated for a physically salient distracter (PSD) condition and a non-salient target-only (TO) condition without any distracter. In the first study, the GBR of N=24 healthy participants were assessed in both conditions and in relation to schizotypal personality traits (SPQ). In the second study, the GBR of N=22 schizophrenia spectrum patients and N=22 matched healthy controls were compared and evaluated in relation to schizophrenia symptoms (PANSS).

Results: Behavioral results in both studies show a significant effect of longer reaction times (RT) and increased error-rates (ER) in the PSD condition as compared to the TO condition. The ER in the patient group is significantly increased. GBR power is significantly increased in the PSD condition as compared to the TO condition in both studies. In the patient study, a higher GBR for schizophrenia patients in the PSD condition ($t = 1.777$; $p = .045$*) and a lower GBR for schizophrenia patients in the TO condition ($t = -1.763$; $p = .046$*) compared with matched healthy controls was observed. The GBR in the PSD condition was significantly correlated with positive SPQ scores ($r = .588$; $p = .0.024$*, Bonferroni corrected) in the first study and with positive ($r = .738$; $p < .0001$*) and disorganized ($r = .690$; $p < .0001$**) PANSS scores, significant after Bonferroni correction).

Conclusions: The aberrant neurophysiological processing of physically salient Stimuli is associated with both, positive schizotypal personality traits, as well as with positive schizophrenia symptoms, especially delusions. The observed abnormalities of sensory processing could be involved in the pathogenesis of delusions.

5.2 German

Hintergrund: In der aktuellen Diskussion um evidenzbasierte psychiatrische Klassifikationen psychischer Erkrankungen wurde vorgeschlagen, das Salienzsyndrom als Hauptsyndrom der Schizophrenie zu betrachten (Os 2009). In der vorliegenden Arbeit wird anormale Salienz (Kapur 2003, 2005) in den Kontext klinischer und neurowissenschaftlicher Herangehensweisen eingeordnet. Eine neue wissenschaftliche Fragestellung bzgl. der Neurophysiologie physikalischer Salienz-wahrnehmung im Gamma-Frequenzbereich wird abgeleitet und experimentell umgesetzt.

Methoden: Die frühe visuell evozierte Gamma-band Antwort (GBR) bei 40Hz wurde in zwei Studien mit einem neu etabliertem visuellem EEG Paradigma gemessen. Die GBR wurde in einer physikalisch salienten Distraktorenbedingung (PSD) und in einer nicht salienten Zielbedingung (TO) ohne Distraktor berechnet. In der ersten Studie wurde die GBR von N =24 gesunden Probanden in Relation zu schizotypischen Persönlichkeitszügen (SPQ) untersucht. In der zweiten Studie wurde die GBR von N =22 Schizophreniespektrum Patienten und N =22 gesunden gematchten Kontrollprobanden verglichen und in Relation zum Schizophrenie Symptomprofil (PANSS) untersucht.

Ergebnisse: Die behavioralen Ergebnisse zeigen in beiden Studien einen signifikanten Effekt längerer Reaktionszeiten (RT) und höherer Fehlerraten (ER) in der PSD Bedingung, verglichen mit der TO Bedingung. In der Patientengruppe war die ER signifikant erhöht. Die GBR in der PSD Bedingung ist in beiden Studien signifikant höher als in der TO Bedingung. In der Patientenstudie zeigte sich für die Patienten eine signifikante höhere GBR in der PSD Bedingung ($t = 1{,}777$; $p = 0{,}045$*) und eine signifikant niedrigere GBR in der TO Bedingung ($t = -1{,}763$; $p = 0{,}046$*) im Vergleich zur Kontrollgruppe. In der ersten Studie korrelierte die GBR in der PSD Bedingung signifikant mit dem positiven SPQ ($r = 0{,}588$; $p = 0{,}024$*, Bonferroni korrigiert) und in der zweiten Studie mit der positiven ($r = 0{,}738$; $p < 0{,}0001$**) und desorganisierten ($r = .690$; $p < 0{,}0001$**) PANSS Subskala, signifikant nach Bonferroni Korrektur.

Schlussfolgerungen: Die veränderte neurophysiologische Verarbeitung physikalisch salienter Reize ist sowohl mit positiven schizotypischen Persönlichkeitsmerkmalen, als auch mit schizophrener Positivsymptomatik, insbesondere Wahn assoziiert. Die gefundenen Anomalien der sensorischen Verarbeitung könnten an der Pathogenese von Wahn beteiligt sein.

6. List of abbreviations

ACC:	Anterior cingulate cortex
AMDP:	Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie *Engl: (German) consortium for methods and documentation in psychiatry*
Amy:	Amygdala
BOLD:	Blood-oxygen-level-dependent
CEN:	Central executive network
CPZ:	Chlorpromazine equivalence dosage
CR:	Conditioned reaction
CS:	Conditioned stimulus
CS -:	Unconditioned neutral comparator stimulus (Jensen et al. 2008)
CSD:	Current source density
dACC:	Dorsal anterior cingulate cortex
dPFC:	Dorsal prefrontal cortex
DMN:	Default mode network
EEG:	Electro-encephalogram
EOG:	Electro-oculography
ER:	Error-rate
ERP:	Event-related potential
FEF:	Frontal eye field
fMRI:	Functional magnetic resonance imaging
GABA:	Gamma-amino-butyric-acid
GBR:	Gamma-band response
Hipp:	Hippocampus
Hypo:	Hypothalamus
Hz:	Hertz
HC:	Matched healthy control group
IPs:	Intraparietal sulcus
JTC:	Jumping to conclusions
LHb:	Lateral habenula
MCT:	Meta-cognitive training
MMN:	Mismatch-negativity
NMDA:	N-methyl-D-aspartame

OFC:	Orbital frontal cortex
PANSS:	Positive and negative syndrome scale
PFC:	Prefrontal cortex
PLF:	Phase-locking factor
PPT:	Pedunculopontine nucleus
PSD:	Physical salient distracter
RT:	Reaction-time
S:	Shell
SN:	Salience network
SN (Fig. 4):	Substantia nigra, pars compacta
SORC:	Stimulus – organism – response – consequence
SPL:	Superior posterior lobule
SPQ:	Schizotypal personality questionnaire
STN:	Subthalamic nucleus
SZ:	Schizophrenia patient group
tACS:	Transcranial alternating current stimulation
tDCS:	Transcranial direct current stimulation
Thal:	Thalamus
TMS:	Transcranial magnetic stimulation
TO:	Target-only
ToM:	Theory of mind
TPJ:	Temporoparietal junction
US:	Unconditioned stimulus
VFC:	Ventral frontal cortex
vmPFC:	Ventral medial prefrontal cortex
VP:	Ventral pallidum
VTA:	Ventral tegmental area

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9. Curriculum vitae

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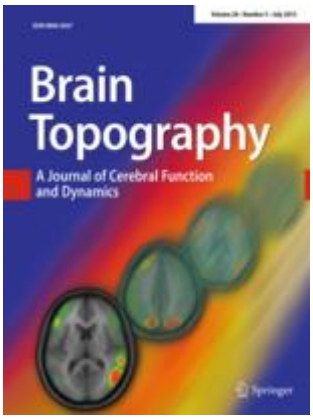
10. Appendix

10.1 Declaration of own contribution on the publication

The personal contribution of Laura Kornmayer on the publications starts with the development of the research questions and the development of the experimental paradigm. Furthermore, all practical aspects of the experiments including recruitment of patients and control participants, as well as assessment of socio-demographical data and EEG recordings were carried out by Laura Kornmayer. The analysis of the obtained EEG data and all statistical analyses also were performed by her. Finally, the conceptualization and writing of the articles was completed by Laura Kornmayer, as well.

10.2 Publication in Brain Topography

Kornmayer L., Leicht G., Mulert C. (2015). Increased gamma oscillations evoked by physically salient distracters are associated with schizotypy. *Brain Topography* **28**, 153-161.



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10.3 Manuscript in revision

Kornmayer L., Leicht G., Mulert C. (2015). Salience related gamma oscillations in schizophrenia are associated with positive and disorganized symptoms. *Manuscript in revision since Feburary, 3rd 2015.*

Original Research Paper

Salience related gamma oscillations in schizophrenia are associated with positive and disorganized symptoms

Dipl.-Psych. Laura Kornmayer[1], Dr. med. Gregor Leicht[1], Prof. Dr. med. Christoph Mulert[1]

Abstract

Background: Aberrant salience in schizophrenia is mainly attributed to excessive dopaminergic reward processing in the ventral striatum (Kapur 2003). In addition, a recent study investigating early sensory processing indicated that increased gamma power evoked by physically-salient stimuli is associated with positive trait schizotypy (Kornmayer et al. 2015). Accordingly, the present study was intended to investigate early processing of physically salient stimuli in patients with schizophrenia.

Methods: The early evoked visual gamma-band response at 40Hz (GBR) was assessed for a schizophrenia patient group (N = 22) and a matched healthy control group (N = 22) applying EEG time-frequency analysis. The evoked GBR was assessed for two conditions within a visual detection paradigm: a non salient target-only condition and a physically-salient distracter condition. GBR power was assessed for both groups and conditions and evaluated in relation to five dimensions of the PANSS symptom score (Van der Gaag, 2006).

Results: A 2 x 2 ANOVA revealed a significant interaction of group and condition for the early visual GBR, with highest power for schizophrenia patients in the physically-salient distracter condition. Moreover, evoked GBR power in this condition was correlated with positive ($r = .738$; $p < .0001$**) and disorganized ($r = .690$; $p < .0001$**) schizophrenia symptoms.

Conclusions: An increase of evoked GBR power during processing of physical salience in schizophrenia was associated with more positive symptoms. We suggest that abnormal processing of physically-salient stimuli might be involved in the pathophysiological genesis of positive symptoms.

11. Statutory declaration / Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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Unterschrift: .....