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Abstract

The mind's ability to create a picture of the world requires the continual processing and integration of huge amounts of different sensory stimuli at every moment. The aim of the present work was to examine the interplay of experiential, neurophysiological, and neurochemical aspects of brain function and to investigate potential differences in the processes between healthy controls (HC) and individuals with schizophrenia (SCZ). In the first study the relationship between multisensory integration in the audiovisual Sound Induced Flash Illusion (SIFI) paradigm, high frequency neural oscillations and the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate were examined. Neurophysiology was assessed by using electroencephalography, and neurotransmitter concentrations were obtained by using proton magnetic resonance spectroscopy. It could be shown that GABA concentration in the superior temporal sulcus (STS) mediates gamma band oscillation power and perception in the SIFI. Furthermore, in the second study the relationship between multisensory processing in the SIFI and event-related potentials (ERPs), as well as beta/gamma band oscillatory activity was assessed. Results did not reveal any behavioral differences in the SIFI illusion rate between SCZ and HC. In the ERPs SCZ compared to HC showed reduced amplitudes and diminished ERP differences between illusion and no-illusion trials. Furthermore, time-frequency representations of oscillatory activity in SCZ revealed a lack of 25-35 Hz oscillatory power enhancement over occipital electrodes. The results suggest that there are multisensory processing alterations in SCZ, however they do not translate on the behavioral level. The third study was focused on the interplay between experiential and neurochemical aspects and examined the relationship between the neurotransmitter glutamate in the STS and occipital cortex and personality traits

in SCZ and HC, measured by the NEO-Five Factory Inventory. The results revealed higher neuroticism and lower extraversion scores and higher STS glutamate concentrations in SCZ compared to HC. Furthermore, data suggested an inverse relationship between STS glutamate concentrations and neuroticism scores in SCZ. Glutamate could hereby be a compensatory mechanism for otherwise enhanced neuroticism trait scores. In summary, in HC a three-fold relationship between the three aspects (experiential, neurophysiological, neurochemical) could be found, whereas in SCZ, only parts of the interactions between the different aspects could be confirmed. The results of this work further the understanding of basic principles of multisensory processing and aims to connect the interplay between different aspects that are present in cortical activity in SCZ and HC.

Zusammenfassung

Um einen Eindruck von der Umgebung zu erzeugen, muss der Verstand kontinuierlich jederzeit riesige Mengen unterschiedlicher Sinneseindrücke verarbeiten und integrieren. Das Ziel der vorliegenden Arbeit war, das Zusammenspiel von erfahrungsbezogenen, neurophysiologischen und neurochemischen Aspekten der Gehirnfunktion zu untersuchen und mögliche Unterschiede in den Prozessen zwischen gesunden Menschen (HC) und Patienten mit Schizophrenie (SCZ) zu erforschen. In der ersten Studie wurde der Zusammenhang zwischen multisensorischer Integration im audiovisuellen Sound Induced Flash Illusion (SIFI) Paradigma, hochfrequenten Oszillationen und den Neurotransmittern Gamma-Amino-Buttersäure (GABA) und Glutamat untersucht. Neurophysiologische Daten wurden mit dem Elektroenzephalogramm erhoben und Neurotransmitterkonzentrationen wurden mit Protonen-Magnetresonanzspektroskopie gemessen. Es konnte gezeigt werden, dass GABA-Konzentrationen im Superioren temporalen Sulcus (STS) Gammaband-Oszillationen Power und Wahrnehmung in der SIFI mediiert. Des Weiteren wurde in der zweiten Studie der Zusammenhang zwischen multisensorischer Verarbeitung in der SIFI und Ereigniskorrelierten Potentialen (ERPs), sowie Beta-/Gammaband-Oszillationen untersucht. Die Ergebnisse ergaben keine Verhaltensunterschiede in der SIFI-Illusionsrate zwischen SCZ und HC. In den ERPs zeigten sich bei SCZ im Vergleich zu HC verringerte Amplituden und verminderte ERP-Unterschiede zwischen Illusions- und Nicht-Illusionstrials. Außerdem offenbarten die Zeit-Frequenz-Analysen der oszillatorischen Aktivität bei SCZ einen Mangel an 25-35 Hz oszillatorischen Powererhöhungen über occipitalen Elektroden. Die Ergebnisse legen nahe, dass es bei SCZ multisensorische Veränderungen gibt, jedoch zeigen sie sich nicht auf der Verhaltensebene. Die dritte Studie fokussierte sich auf das Zusammenspiel

zwischen Verhaltens- und neurochemischen Aspekten und untersuchte den Zusammenhang zwischen dem Neurotransmitter Glutamat im STS und im occipitalen Cortex und Persönlichkeitsmerkmalen bei SCZ und HC, gemessen mit dem NEO-Fünf-Faktoren-Inventar. Die Ergebnisse offenbarten höhere Neurotizismus- und niedrigere Extraversionswerten, sowie höhere STS Glutamatkonzentrationen bei SCZ im Vergleich zu HC. Darüber hinaus wiesen die Daten auf einen umgekehrten Zusammenhang zwischen STS Glutamatkonzentrationen und Neurotizismuswerten bei SCZ hin. Glutamat könnte dabei ein Kompensationsmechanismus für andernfalls erhöhte Neurotizismusmerkmalswerte sein. Zusammengefasst konnte bei HC ein dreifacher Zusammenhang zwischen den drei Aspekten (erfahrungsbezogen, neurophysiologisch, neurochemisch) gefunden werden, während bei SCZ nur Teile der Interaktionen zwischen den verschiedenen Aspekten bestätigt werden konnten. Die Ergebnisse dieser Arbeit erweitern das Verstehen der grundlegenden Prinzipien multisensorischer Verarbeitung und zielen darauf ab, das Zusammenspiel zwischen verschiedenen Aspekten, die in der kortikalen Aktivität bei SCZ und HC vorhanden sind, miteinander zu verbinden.

Index

1. Personal contributions to the individual publications

Study 1: Balz, J., Keil, J., Roa Romero, Y., Mekle, R., Schubert, F., Aydin, S., Ittermann, B., Gallinat, J. & Senkowski, D. (2016). GABA concentration in superior temporal sulcus predicts gamma power and perception in the sound-induced flash illusion. *NeuroImage, 125*, 724-730.

- First authorship
- Substantial involvement in planning, conceptualization, preparation and organization of the experiment
- Literature research
- Substantial involvement in study design
- Recruitment of participants and main investigator (shared with Yadira Roa Romero)
- Leading data acquisition of experiential and neurophysiological data (EEG) (shared with Yadira Roa Romero), attendance at acquisition of neurochemical data (MRS)
- Leading data preprocessing and statistical analysis
- Main responsibility for presentation and discussion/interpretation of results
- Leading drafting/writing the manuscript
- Main responsibility for publishing the manuscript

Study 2: Balz, J., Roa Romero, Y., Keil, J., Krebber, M., Niedeggen, M., Gallinat, J., & Senkowski, D. (2016). Beta/Gamma oscillations and event-related potentials indicate aberrant multisensory processing in schizophrenia. *Frontiers in Psychology, 7*, 1-12.

- First authorship
- Substantial involvement in planning, conceptualization, preparation and organization of the experiment
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- Recruitment of participants and main investigator (shared with Yadira Roa Romero)
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- Leading data preprocessing and statistical analysis
- Main responsibility for presentation and discussion/interpretation of results
- Leading drafting/writing the manuscript
- Main responsibility for publishing the manuscript

Study 3: Balz, J., Roa Romero, Y., Keil, J., Schubert, F., Ittermann, B., Montag, C., Gallinat, J., & Senkowski, D. (2017). *Glutamate concentration in the superior temporal sulcus relates to neuroticism in schizophrenia.* Manuscript submitted for publication.

- First authorship
- Substantial involvement in planning, conceptualization, preparation and organization of the experiment
- Literature research
- Substantial involvement in study design
- Recruitment of participants and main investigator (shared with Yadira Roa Romero)
- Leading data acquisition of experiential data (shared with Yadira Roa Romero), attendance at acquisition of neurochemical data
- Leading data preprocessing and statistical analysis
- Main responsibility for presentation and discussion/interpretation of results
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Dipl.-Psych. Johanna Balz

2. Introduction and theoretical background

The mind's ability to create a picture of the world requires the continual processing and integration of huge amounts of different sensory stimuli at every moment. When we walk across a market we can see the variety of colors and shapes of all kinds of fruits, we hear the marketers advertising their goods, we smell the scent of the oranges, and feel the texture of the fruit we pick up with our hands. We use our senses, especially our eyes and ears, to perceive and process this information and combine it to a coherent percept of our environment. How does the integration of input from multiple sources in our brains work? And what happens when this highly complex interplay of different neural processes is disturbed?

2.1 Synchronized oscillations as precondition for successful multisensory integration

Several studies face the issue of how multisensory processing functions on a behavioral level (e.g., Shams, Kamitani, & Shimojo, 2000; Stein, London, Wilkinson, & Price, 1996) and furthermore, what neural mechanisms are operating in the human brain to generate successful multisensory integration (e.g., Senkowski, Saint-Amour, Gruber, & Foxe, 2008). Rhythmic neuronal activity patterns in the human brain, so-called neural oscillations, as obtained by electrophysiological measurements, can provide insights about neuronal communication (Singer & Gray, 1995; Singer, 1999). Fries (2005) states that communication between neuronal groups depends on coherence between them. Neuronal coherence may thus be a key mechanism underlying successful neuronal communication and multisensory integration. How do neuronal populations communicate with each other? Neural oscillations

reflect rhythmic excitability fluctuations that create temporal windows for communication (Gips, van der Eerden, & Jensen, 2016). Coherent oscillating neuronal groups have opened their communication windows for in- and output at the same time and are therefore able to communicate effectively.

Synchronized oscillations are a functional mechanism for flexible communication within and between cortical areas (Uhlhaas, Haenschel, Nikolić, & Singer, 2008). Oscillatory phase synchrony with precise temporal relationships has been associated with feature binding and may be important for cognitive functions like attention, working memory, subsystem integration, perceptional grouping and consciousness (Uhlhaas & Singer, 2010; Uhlhaas et al., 2006, 2008). Recently, studies have provided evidence that synchronized oscillations are not only important for unisensory perception but also for successful neuronal communication in multisensory perception (Engel, Senkowski, & Schneider, 2012; Kayser & Logothetis, 2009; Keil, Müller, Hartmann, & Weisz, 2014; Lakatos, Chen, O 'Connell, Mills, & Schroeder, 2007; Maier, Chandrasekaran, & Ghazanfar, 2008; Senkowski, Schneider, Foxe, & Engel, 2008). For example, Lakatos et al. (2007) have shown the relationship between oscillations and audiovisual multisensory integration in animals and Keil et al. (2014) reported a relationship between oscillatory synchrony and multisensory activity during the Sound Induced Flash Illusion (SIFI) paradigm. Furthermore, there is evidence that neural coherence is linked to processing between unisensory and multisensory areas (Hummel & Gerloff, 2005; Maier et al., 2008). The important role of neural synchrony in multisensory integration has been studied by Ghazanfar et al. (2013). They found evidence that coupled oscillatory activity connects the neuronal signals across uni- and multisensory brain regions, which can be a sign for crossmodal information matching. In multisensory integration, coherent oscillations can be found especially in the higher frequency ranges, i.e. the beta

band (15-30 Hz; Hipp, Engel, & Siegel, 2011; Schepers, Schneider, Hipp, Engel, & Senkowski, 2013; Senkowski, Molholm, Gomez-Ramirez, & Foxe, 2006) and gamma band range (30-100 Hz; Arnal, Wyart, & Giraud, 2011; Schneider, Lorenz, Senkowski, & Engel, 2011; Senkowski, Herrmann, & Woldorff, 2005; Senkowski, Kautz, Hauck, Zimmermann, & Engel, 2011).

2.2 The association cortex - specific brain areas for different sensory modalities

Multisensory processes can combine the information of different senses by taking different functions into account, e.g. attention, memory, semantic analysis, anticipation and intention and principle mechanisms like temporal synchrony (e.g., Uhlhaas et al., 2008). Information from different sensory modalities can be complementary, redundant or conflicting. There are multisensory interactions in the brain that compare whether the sensory inputs are matching and can be processed together or whether they are conflicting and have to be integrated. Thus, multisensory integration works as a dynamic interplay between different neural populations and brain areas, and multisensory information is processed in different parts of the brain (Ghazanfar & Schroeder, 2006). For instance, acoustic information is processed in auditory areas in the temporal lobe and visual information in visual areas in the occipital cortex (OCC), but there are also multisensory regions that integrate information from the primary regions, such as the superior temporal lobe, encompassing the superior temporal gyrus and the superior temporal sulcus[1] (STS; Calvert, 2001; Maier et al., 2008).

[1] In the following chapters I will mainly refer to the "STS", however we measured a voxel encompassing both the superior temporal sulcus and the superior temporal gyrus, i.e. the association cortex includes both structures.

The STS is involved in integrating behaviorally relevant audio-visual information (Barraclough, Xiao, Baker, Oram, & Perrett, 2005; Hietanen & Perrett, 1996). It is also implicated in processes like the Theory of Mind (Beauchamp, 2015), speech perception and processing (Vaden, Muftuler, & Hickok, 2010; Vander Ghinst et al., 2016) and the perception of emotional stimuli (Radua et al., 2010). The structures of the superior temporal lobe are furthermore associated with personality traits (Li et al., 2017). Some studies have suggested that those structures in the association cortex are presumably altered in individuals with autism disorder (Jou, Minshew, Keshavan, Vitale, & Hardan, 2010) and schizophrenia (Kasai et al., 2003).

2.3 The central role of gamma-aminobutric acid and glutamate for information transfer in the brain

High frequency oscillatory activity is especially influenced by the neurotransmitter Gamma-AminoButryc Acid (GABA), which primarily acts in inhibitory neurotransmission. Studies support the assumption of a relationship between GABA and neural synchronization (Allman et al., 2008; Mann & Paulsen, 2007; Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009; Traub et al., 2003). For example, Traub et al. (2003) reported that gamma band oscillations are modulated by GABA in the hippocampus of rats. Mann and Paulsen (2007) emphasized the importance of GABAergic mechanisms for the generation of cortical rhythms in the hippocampus. They suggest that synaptic inhibition can be synchronized by interactions with GABAergic and excitatory neurons. A magnetic resonance spectroscopy (MRS) study by Muthukumaraswamy et al. (2009) in human participants showed that across individuals gamma oscillations are positively correlated with resting GABA concentration in the visual cortex. Furthermore, it has been suggested that multisensory effects can be modulated by GABA antagonism (Allman et al., 2008).

Consequently, there could be a link between the three factors GABA concentration, multisensory processing, and oscillatory activity (**study 1**).

The generation of gamma band oscillations (GBO) is not only driven by GABA neurotransmission (Bartos, Vida, & Jonas, 2007; Buzsáki & Wang, 2012), but also by the activation of metabotropic glutamate receptors (Bartos et al., 2007; Whittington, Traub, & Jefferys, 1995). Hence, differences in the glutamatergic systems might contribute to individual differences in multisensory processing. Glutamate serves as the primary excitatory neurotransmitter in the nervous system and is as such involved in many processes like neurodevelopment and neurodegeneration (Meldrum, 2000). Impaired function in the glutamatergic system may furthermore be a contributory factor in schizophrenia (SCZ; Coyle, 1996; Javitt & Zukin, 1991), a hypothesis that I will elaborate in **chapter 6**.

2.4 Aberrant neurophysiological and neurochemical processes in schizophrenia

Sensory processing does not always function flawlessly. Particularly in patients with schizophrenia, the interplay between the different brain areas might be disturbed due to aberrant connectivity (Friston, 1999). Furthermore, altered neural oscillations can lead to decreased coherence: Uhlhaas and Singer (2010) stated that abnormal synchronization of beta and gamma band activity influences the pathophysiology of schizophrenia and leads to cognitive deficits in memory, perception and consciousness, and other symptoms. For example dysfunctional coordination of neural activity may lead to a deficit in Gestalt perception (Uhlhaas et al., 2006). Uhlhaas et al. (2006) report that schizophrenic patients are significantly impaired in detecting images in which the elements need to be grouped into coherent object representations. A study by Gruetzner et al. (2013) showed abnormal high-frequency oscillations in individuals with schizophrenia during visual processing of Mooney

faces. Additionally, Sun et al. (2013) tested medication-naïve, first episodes schizophrenia patients and found evidence for dysregulated beta and gamma oscillations during sensory processing of unisensory visual stimuli. Furthermore, Senkowski and Gallinat (2015) suggested that abnormal gamma-band oscillations might be linked to deficits in working memory and cognition.

Several studies have reported altered neural oscillations in unisensory paradigms (Gallinat et al. 2004; Haenschel et al. 2009; Leicht et al. 2010/2011; Popov et al., 2015; Spencer et al. 2004; Uhlhaas et al., 2006). It is possible that altered oscillatory activity extends beyond unisensory paradigms into multisensory processing (de Jong, Hodiamont, Van den Stock, & de Gelder, 2009; Ross et al., 2007; Stekelenburg, Maes, Van Gool, Sitskoorn, & Vroomen, 2013; Szycik et al., 2013; Tseng et al., 2015). Further exploration of this important because long-range oscillatory information transfer required by multisensory processing is likely to show up hypothesized oscillatory connectivity deficits in schizophrenia (**study 2**).

The studies that have examined multisensory processing in SCZ support this notion (de Jong et al., 2009; Ross et al., 2007; Stekelenburg et al., 2013; Szycik et al., 2013; Tseng et al., 2015). For example, Stekelenburg et al. (2013) presented congruent and incongruent audiovisual stimuli to schizophrenic and healthy participants in an event-related potential study. They observed that participants with schizophrenia have deficits in the audiovisual integration network, which could be a sign of disturbed multisensory integration in schizophrenia.

Another aspect of schizophrenic psychopathology is seen in extremes of particular personality traits (Berenbaum & Fujita, 1994; Boyette et al., 2013; Camisa et al., 2005; Compton et al., 2015; Gurrera, Nestor, & O'Donnell, 2000; Kirihara et al., 2012; Ohi et al., 2016). Schizophrenia is related to altered glutamate concentrations in several regions of the

brain (Marsman et al., 2013; Merritt, Egerton, Kempton, Taylor, & McGuire, 2016; Poels et al., 2014; Wijtenburg, Yang, Fischer, & Rowland, 2015), consequently there might be a link between experiential aspects, like perception, behavior or personality, and altered glutamate concentrations in SCZ (**study 3**).

SCZ is also linked to alterations in the GABA system (Uhlhaas & Singer, 2012). Since GABA could play a role in multisensory integration (Allman et al., 2008; Hoshino, 2012, 2014), one could speculate that alterations in the GABA system might contribute to multisensory processing deficits in schizophrenia (Cloke & Winters, 2015).

3. Aims and general methods

The following chapters provide insight into the main research questions of the studies that were conducted for this thesis. In general, the work focused on the interplay between three different aspects: 1. the experiential aspect (perception, behavior, personality, i.e. multisensory processing, Big Five), 2. the neurophysiological aspect (electroencephalography, i.e. event-related potentials (ERPs), oscillations), and 3. the biochemical aspect (neurotransmitter concentrations, i.e. GABA, glutamate), both in healthy individuals and in patients with schizophrenia (SCZ) patients[2] (**Figure 1**).

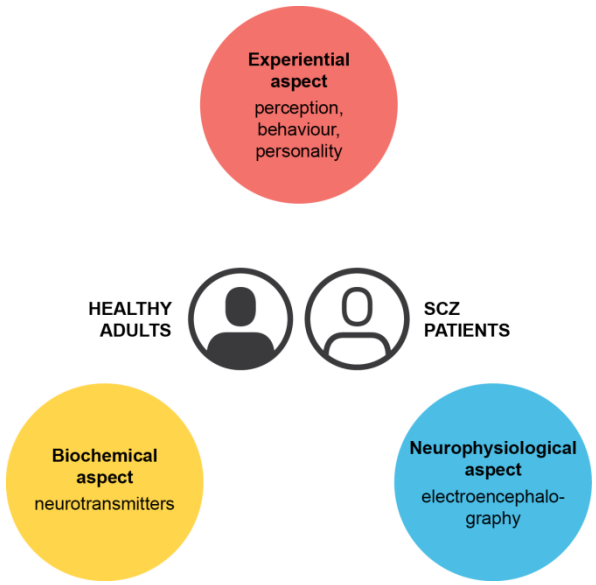

Figure 1: Outline of the overarching research question. The studies focused on the interplay of the triangle consisting of experiential aspects (red circle), neurophysiological aspects (blue circle) and biochemical aspects (yellow circle). Study 1 was conducted with a sample of healthy adults, in study 2 and study 3 a SCZ patient group was compared with a healthy control group.

[2] The conducted studies were approved by the Medical Ethics Comitee of the Charité University Medicine Berlin and were conducted in accordance with the Declaration of Helsinki. All participants gave informed consent to participate in the study.

In the first study I[3] focused on the interplay between all three aspects in healthy participants (**chapter 4**), in study 2 I assessed experiential and neurophysiological aspects in SCZ patients and compared them to a healthy control group (**chapter 5**), and in study 3 I examined the relationship between experiential and biochemical aspects in SCZ compared to HC (**chapter 6**).

3.1 Perception, behavior & personality

In order to explore multisensory integration processes, the SIFI paradigm was applied. The SIFI is a well established paradigm to investigate the influence of auditory input on visual perception. In this paradigm, a single visual flash concurrently presented with two brief auditory tones can create the illusory percept of a second flash (Shams et al., 2000). Hence, the SIFI paradigm enables the comparison of physically identical audiovisual stimuli that are either not integrated (which results in the perception of one flash), or integrated (which results in the perception of two flashes). The illusion rate provides a picture of how the integration process works, which can be individually different for each participant. Furthermore, the SIFI is a universally functioning paradigm in which no particular language knowledge is necessary and which even persists when the participant is made aware of the illusion (Rosenthal, Shimojo, & Shams, 2009), which makes it an ideal behavioral paradigm to test for basic integration processes.

[3] The word "I" is used throughout in the sense that I was principally responsible for each stage of the experiments, but of course relied extensively upon the support of collaborators, namely the research group for Multisensory Integration and the Physikalisch-Technische Bundesanstalt, Berlin. For precise details of individual contributions see chapter 1.

The experimental design closely resembled the setup used by Mishra et al. (2007). The experiment was conducted in a sound-attenuated, electrically shielded chamber. Subjects maintained fixation on a central cross on a screen. Auditory stimuli were delivered from a speaker beneath the screen. Visual stimuli, consisting of a white uniform disk, were presented in the visual periphery (Shams, Kamitani, & Shimojo, 2002). The participants' task was to attend to the stimuli and to report how many flashes they perceived by pressing one of three response buttons (0, 1 or 2 flashes) (**Figure 2A**).

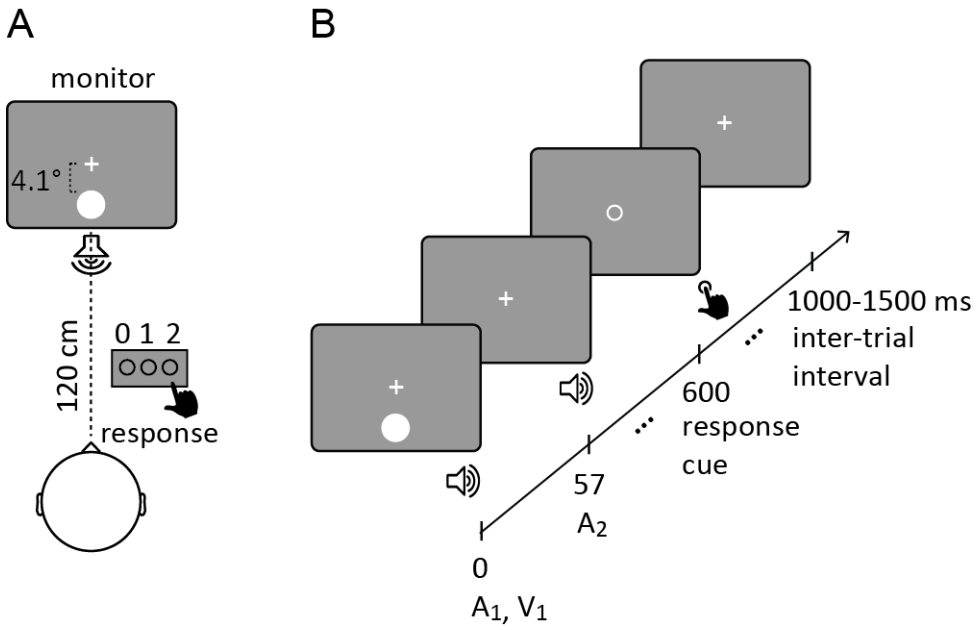

Figure 2: (A) Schematic overview of experimental setup. (B) Schematic representation of a critical trial during the SIFI paradigm. One single visual stimulus (V1) is combined with two auditory stimuli (A1, A2).

The SIFI experiment consisted of 6 conditions with altogether 1050 trials. The critical trial, a combination of 2 auditory and 1 visual stimuli, can be seen in **Figure 2B**. The 300 critical trials and the 150 trials per control condition were presented in random order in 8 blocks

with 132 trials each. The total runtime of the experiment was 44 minutes. The experiments were programmed with MATLAB, using the PsychToolbox.

Adult participants between the ages of 18 and 55 years were recruited. Keeping this age range minimized the chance of confounds relating to age-extremes. Before the experiments, all participants were screened for mental disorders with the German version of the Structural Clinical Interview for DSM-IV-TR (SCID; First, Spitzer, Gibbon, & Williams, 2002). Personality traits were assessed with the NEO-Five Factory Inventory (NEO-FFI; Costa & McCrae, 1989, 1992). The NEO-FFI measures the so called “Big Five”, consisting of neuroticism (N), extraversion (E), openness (O), agreeableness (A) and conscientiousness (C) (Costa & McCrae, 1989, 1992). Costa and McCrae (1992) defined (N) as the vulnerability to emotional instability and self-consciousness, (E) as the predisposition towards sociability, assertiveness and social interaction, (O) as the cognitive disposition to creativity and aesthetics, (A) as the tendency towards being sympathetic, trusting and altruistic, and (C) as the tendency towards dutifulness and competence. Additionally, the Brief Assessment of Cognition in Schizophrenia (BACS) was assessed to measure the cognitive performance of the schizophrenic patients and healthy individuals (Keefe et al., 2004). In SCZ patients, I used the Positive and Negative Syndrome Scale (PANSS) to assess the severity of acute psychotic symptoms (Kay, Fiszbein, & Opler, 1987). All participants reported demographic information and information about their eyesight. The hearing capabilities were measured with an audiogram. A random sample of 40 % of all participants underwent a multi-drug screening test to prevent any substance-induced interferences with neurophysiological or biochemical data.

3.2 Neurophysiology

Neurophysiological data were assessed with an electroencephalogram (EEG). The EEG is the standard noninvasive method to measure electrical potential changes arising from the brain (Senkowski, Schneider, et al., 2008). The EEG reflects the summed postsynaptic activity in the underlying cortical regions (Luck, 2005). EEG was recorded using a 128-channel active system (EasyCap, Herrsching, Germany), including one horizontal and one vertical EOG electrode placed near the right outer canthus and below the right eye. Data were recorded against nose reference with a pass band of 0.016-250 Hz and digitized at a sampling rate of 1000 Hz. Pre-processing and offline data analysis were performed using EEGlab (Delorme & Makeig, 2004), Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011), and custom-made Matlab scripts (MathWorks, Natick, MA).[4] These enabled a wide range of quantitative measures to extract information from the recordings, including ERPs to measure the averaged early response to stimuli and time-frequency analyses (Tallon-Baudry & Bertrand, 1999), to examine the fluctuations in oscillatory power (Rockstroh, 1982).

3.3 Biochemistry

I used proton magnetic resonance spectroscopy (MRS) to examine GABA and glutamate concentrations. MRS is a non-invasive technique to determine the relative concentrations of certain metabolites in vivo in a specific voxel of interest in the human brain by using the magnetic resonance signal of hydrogen (Harris, Saleh, & Edden, 2017).

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[4] The methods of the 3 studies are shortly summarized in this chapter. For more methodical details concerning SIFI, EEG and MRS acquisition and analyses see the full manuscripts provided in the Appendices A-C.

The MRS measurements were conducted in cooperation with the Physikalisch Technische Bundesanstalt (PTB) in Berlin. Neurotransmitter concentrations were assessed in two voxels: the left STS and the OCC (**Figure 3**). The volume of interest for a single voxel MRS was 20 x 30 x 20 mm^3 for the STS and 30 x 20 x 20 mm^3 for the OCC voxel. We used the SPECIAL sequence (Mekle et al., 2009; Schubert, Kühn, Gallinat, Mekle, & Ittermann, 2017) for obtaining glutamate concentrations in the STS and OCC voxel and MEGAPRESS (Edden, Intrapiromkul, Zhu, Cheng, & Barker, 2012; Mescher, Merkle, Kirsch, Garwood, & Gruetter, 1998) for assessing GABA concentrations in the STS.

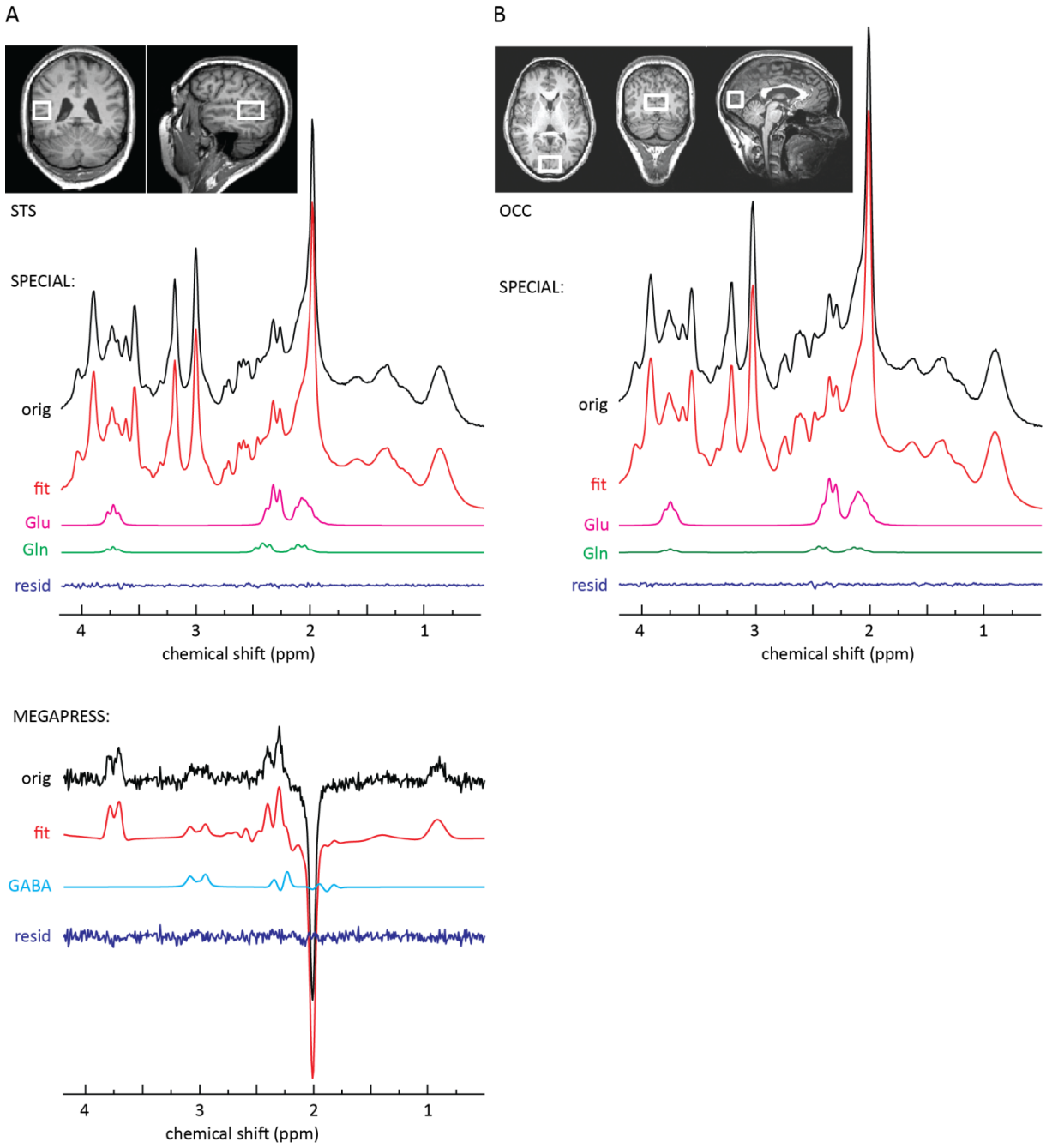

Figure 3: Sample magnetic resonance spectra from the left STS voxel (A) and the OCC voxel (B). The upper panel illustrates the location of the voxel on T1-weighted images. The top row of each panel represents the original SPECIAL or MEGA-PRESS spectrum. Also shown are theoverall fits and the fitted components of interest. The small residuals reflect the high quality of the fits. Right: same for the OCC voxel.

4. Study 1: Do differences in the GABA system contribute to individual differences in high-frequency oscillations in multisensory processing?

Research question and method:

It has been stated that GBO play a role in multisensory processing (Hipp et al., 2011; Lakatos et al., 2007; Senkowski et al., 2011). In addition, studies have provided evidence that the GABAergic system is involved in the generation of high frequency oscillations (Allman et al., 2008; Bartos et al., 2007; Mann & Paulsen, 2007; Muthukumaraswamy et al., 2009; Sohal, Zhang, Yizhar, & Deisseroth, 2009; Traub et al., 2003). However, it is yet unknown whether there is a link between the concentration of resting GABA, oscillatory activity and audiovisual perception in healthy adults (**Figure 4**). There are two recent studies about the relationship between resting GABA concentrations and gamma oscillations in unisensory visual stimulation. The studies contradict each other in their results: Muthukumaraswamy et al. (2009) found a link between GABA concentration and stimulus-induced gamma oscillations, whereas Cousijn et al. (2014) did not find such a relationship. Therefore it was of particular interest to test the relationship between GABA concentration and gamma oscillations in a multisensory paradigm.

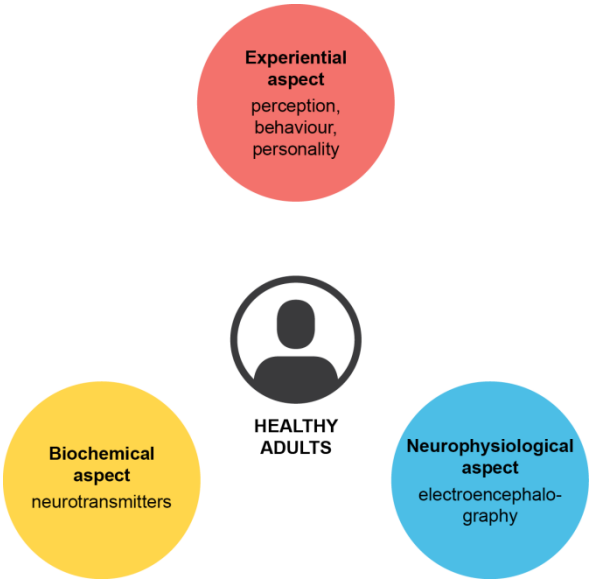

Figure 4: **Research question of study 1.** The study focused on the interplay between the SIFI illusion rate (red circle), high frequency oscillations (blue circle), and GABA or glutamate concentrations in the left STS (yellow circle) in healthy adults.

In this experiment (manuscript no. 1: Balz, Keil, Roa Romero, Mekle, Schubert, Aydin, Ittermann, Gallinat, & Senkowski, 2016, **Appendix A**) I examined neural synchronization during the SIFI paradigm in 39 healthy adults. During the SIFI task, EEG data of the participants were recorded. I presented six stimulus combinations, consisting of 0, 1 or 2 auditory stimuli, combined with 0, 1 or 2 visual stimuli (for setup details see ***chapter 3.1***). The participants' task was to report the number of perceived visual stimuli by pressing a button. The runtime of the experiment was 44 minutes but participants could take breaks in between the blocks, so that the recording of data took ca. 90 minutes per participant.

Furthermore, on a separate day within 48 hours after the EEG measurement, every participant took part in an MRS measurement to analyze the neurotransmitters GABA and glutamate in the STS. I then studied the correlation between the resting GABA and

glutamate concentrations and the synchronized EEG activity in the predefined voxel, and the performance in the SIFI task.

I developed the following research question:

Is there a relationship between multisensory processing, EEG activity, and GABA concentrations in healthy adults?

Working hypotheses:

- I expected a replication of behavioral effects of a bistable percept of the SIFI illusion in the critical A_2V_1-trials (Keil et al., 2014; Shams et al., 2000).
- I hypothesized that the behavioral effect is paralleled by a modulation of high frequency oscillatory activity, which is presumably localized to primary sensory (i.e. visual cortex) and higher order cortical areas (i.e. STS) (Mishra et al., 2007).
- I assumed that there is a positive correlation between the amount of GABA, the oscillatory activity and the number of illusion percepts.

Main Results:

In the critical trials consisting of two auditory and one visual stimulus (SIFI trials), participants reported an illusory second flash in 65 % of the trials. In the SIFI trials I found robust GBO power enhancements at central electrodes (**Figure 5**).

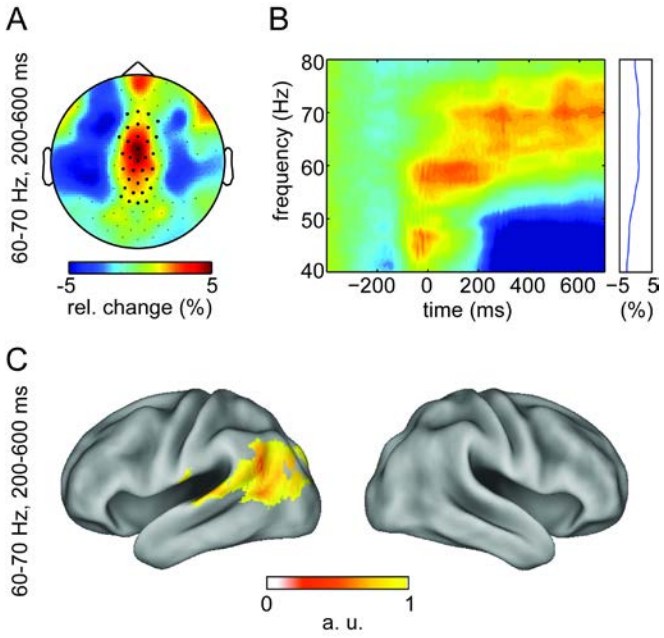

Figure 5: Gamma band oscillations in the sound-induced flash illusion. (A) Topography of GBO power change in response to SIFI stimuli, in which a single flash is presented alongside two rapidly repeating tones. The bold dots highlight the cluster of electrodes for which a significant post-stimulus power increase relative to baseline was found in the 200 to 600 ms period. (B) Time–frequency representation (TFR) of relative power changes for the central electrode cluster depicted in (C). (C) GBO power was source-localized in the left STS and extrastriate cortex. The figure was masked at a 0.85 threshold relative to the maximum. a.u. = arbitrary units.

GBO power in the left STS and GABA concentration correlated with the illusion rate (**Figure 6**). Moreover, I found a strong positive correlation between GABA concentration and GBO power.

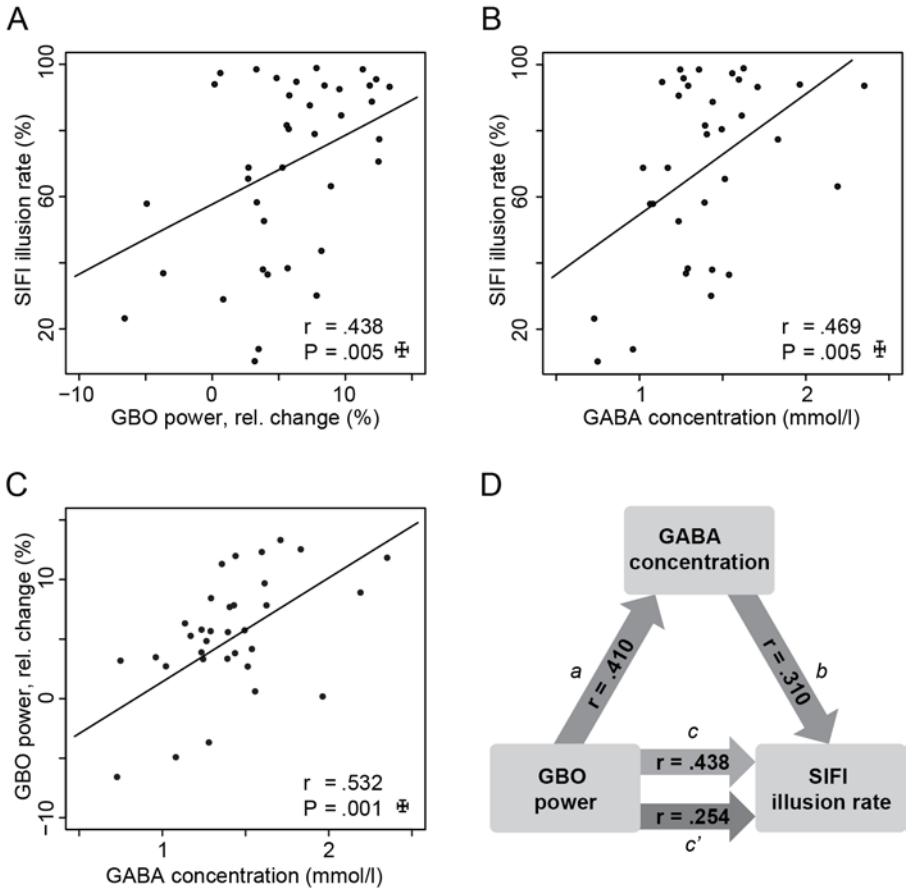

Figure 6: GABA concentration shapes audiovisual perception via its influence on gamma band oscillations. (A) Source-localized GBO power in the STS is positively correlated with the SIFI illusion rate (N = 39). (B) and (C) GABA concentration in the STS correlates with SIFI illusion rate and GBO power, respectively (N = 34). (D) Path analysis reveals that GABA concentration mediates the positive correlation between GBO and the SIFI illusion rate. Path (a) reflects the coefficient for the effect of GBO power on GABA concentration. Path (b) reflects the coefficient for the effect of GABA concentration on the illusion rate. Paths (c) and (c′) reflect the coefficients for the total and direct effects (i.e., with (c) and without (c′) the contribution from GABA) of GBO on SIFI illusion rate, respectively. A bootstrapping test, which involved 34 participants for whom all three measures were available, revealed significant differences between the effects of paths (c) and (c′).

Relevance of the results:

My findings provide strong evidence that the GABA level shapes individual differences in audiovisual perception through its modulatory influence on GBO (**Figure 7**). Furthermore, my results add clarification to the controversy regarding the relationship between visual high-frequency oscillations and GABA concentrations (Cousijn et al., 2014; Muthukumaraswamy et al., 2009) by confirming a positive correlation between GBO and GABA concentrations. Like Cousijn et al. (2014), I did not find any correlations between GBO and the neurotransmitter glutamate. Furthermore my results extend previous findings about the relationship between oscillatory activity and unisensory processing by using a multisensory paradigm. I could show for the first time that there is a three-fold relationship between the SIFI illusion rate, GBO power and GABA concentration in the STS. The remaining question regards the processes that occur in the brain when this interplay is out of balance, which I will refer to in the next chapters.

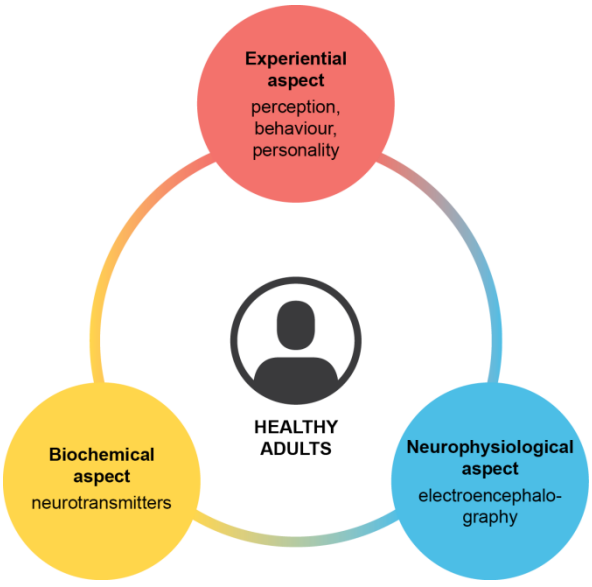

Figure 7: Finding of study 1. In healthy adults SIFI illusion rate (red circle) is linked to GBO power (blue circle) and GABA concentration in the left STS (yellow circle). My results show a three-fold relationship between experiential, neurophysiological and biochemical aspects in healthy individuals.

5. Study 2: Do aberrant neural oscillations underlie multisensory processing deficits in schizophrenia?

As shown in the previous chapter, oscillatory activity plays a role in the processing of multisensory stimuli. I decided to conduct the SIFI paradigm not only with healthy individuals but also with schizophrenic patients, in order to find out if they show differences in the perception and processing of multisensory information and if those processing differences are visible in ERPs and oscillatory activity (**Figure 8**).

Research questions and method:

From a clinical perspective, behavioral studies suggest a link between impaired multisensory processing and psychopathology. Especially in individuals with schizophrenia, behavioral studies have discovered specific deficits in cognition and behavior (de Jong et al., 2009; Martin, Giersch, Huron, & van Wassenhove, 2013). There is also evidence that in patients with schizophrenia oscillatory activity is altered in unisensory paradigms (Fujimoto et al., 2012; Spencer, Salisbury, Shenton, & McCarley, 2008). Thus, there may be a link between impaired oscillatory activity and multisensory processing in SCZ (e.g., Stekelenburg et al., 2013).

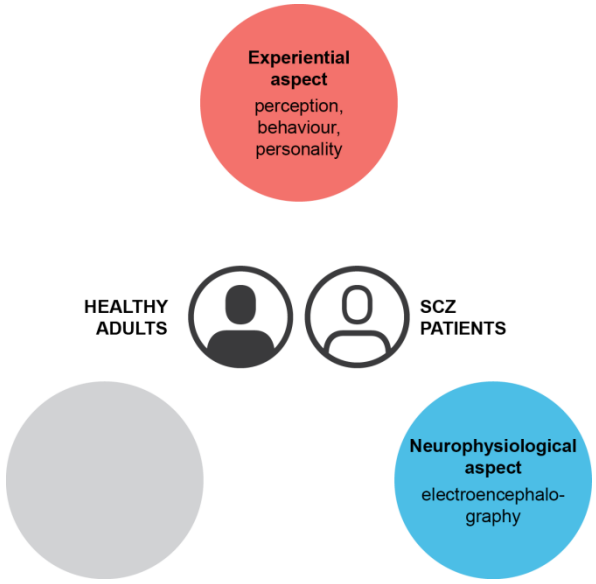

Figure 8: Research question of study 2. The study focused on the interplay between the SIFI illusion rate (red circle) and the neurophysiological aspects ERPs and high frequency oscillations (blue circle) in SCZ patients and a healthy control group.

In this experiment (manuscript nr. 2, Balz et al. 2016, **Appendix B**), I compared multisensory processing and neuronal synchronization in the SIFI paradigm between SCZ patients and a healthy control (HC) group. The experimental design of the SIFI paradigm and for EEG data recording was identical to the design in study 1 (description in **chapter 3.1**). For the final data analysis, 15 patients with schizophrenia were compared to the 15 best matching HC, matched for age, gender, education and amount of cigarettes per day.

I posed the following research question:

Is there a relationship between multisensory processing and oscillations in SCZ?

Working hypotheses:

- I predicted a behavioral effect, visible in a different rate of illusory percepts in patients compared to the healthy control group in the SIFI paradigm.

- I hypothesized that patients differ from healthy participants in the processing of multisensory information, visible in differences in ERPs (Stekelenburg et al., 2013).
- I expected a modulation of oscillatory activity, which is presumably localized to primary sensory (i.e. visual cortex) and higher order cortical areas (i.e. STS), with aberrations in SCZ.

Main results:

Contrary to the first hypothesis, on the behavioral level, the multisensory illusion rates (perception rates) did not significantly differ between SCZ patients (55.7 %) and healthy controls (55.4 %). The analysis of the ERP data showed reduced ERP amplitudes and diminished ERP differences between illusion and no-illusion trials in SCZ compared to HC (**Figure 9**, depiction of multisensory trials). Furthermore, the TFRs of oscillatory activity revealed altered 25-35 Hz oscillatory power over occipital electrodes in SCZ. In HC I could observe an early enhancement of 25-35 Hz total power for illusion trials compared to no-illusion trials in the time window of 100-150 ms after stimulus onset, which was lacking in SCZ (**Figure 10**, depiction of multisensory TFRs).

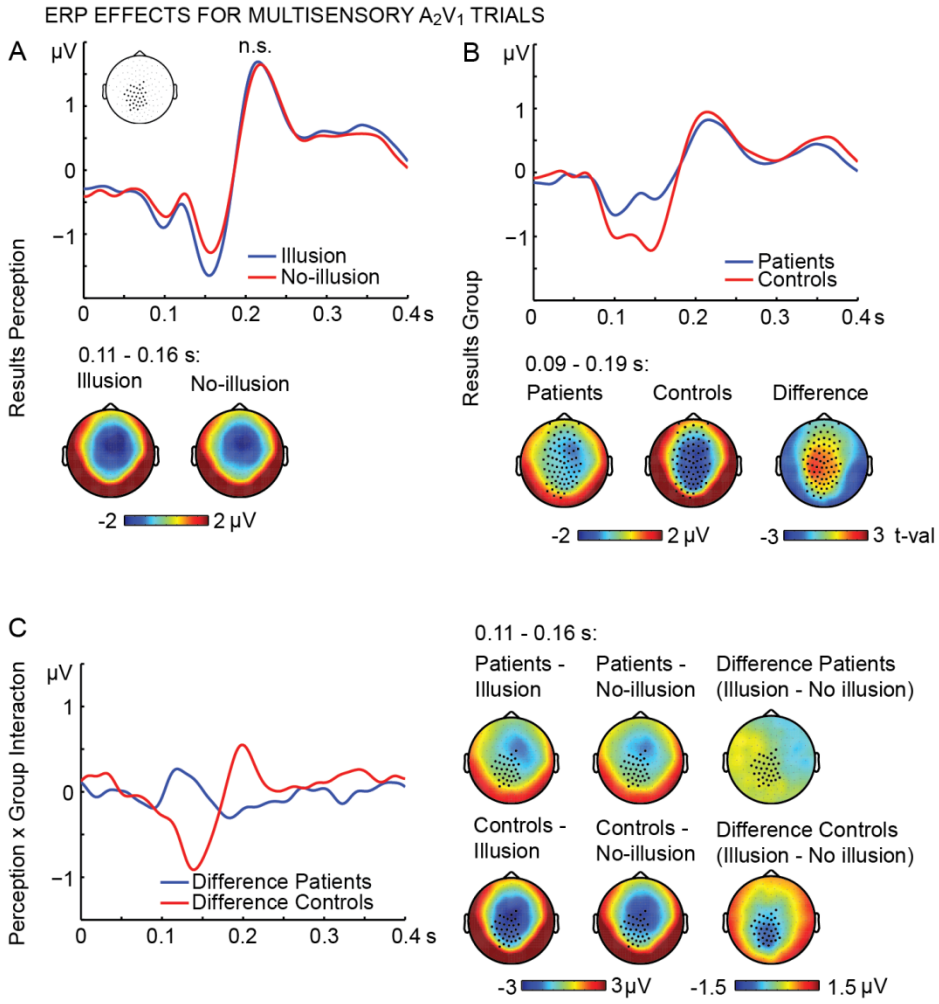

Figure 9: ERP effects of multisensory (A_2V_1) trials. Outcome of the comparisons between Perceptions (illusion vs. no-illusion), between Groups (SCZ vs. HC), and for the Perception differences between Groups (i.e., the Perception by Group interaction). The upper planes in panels (A–B) and the left plane in panel (C) illustrate the ERP results for Perception (A), the main effect of Group (B), and the Perception by Group interaction (C). The lower planes (A-B) and right plane (C) depict topographic maps for the observed results with highlighted significant cluster electrodes. Time-point 0 indicates the onset of the first auditory and visual stimulus.

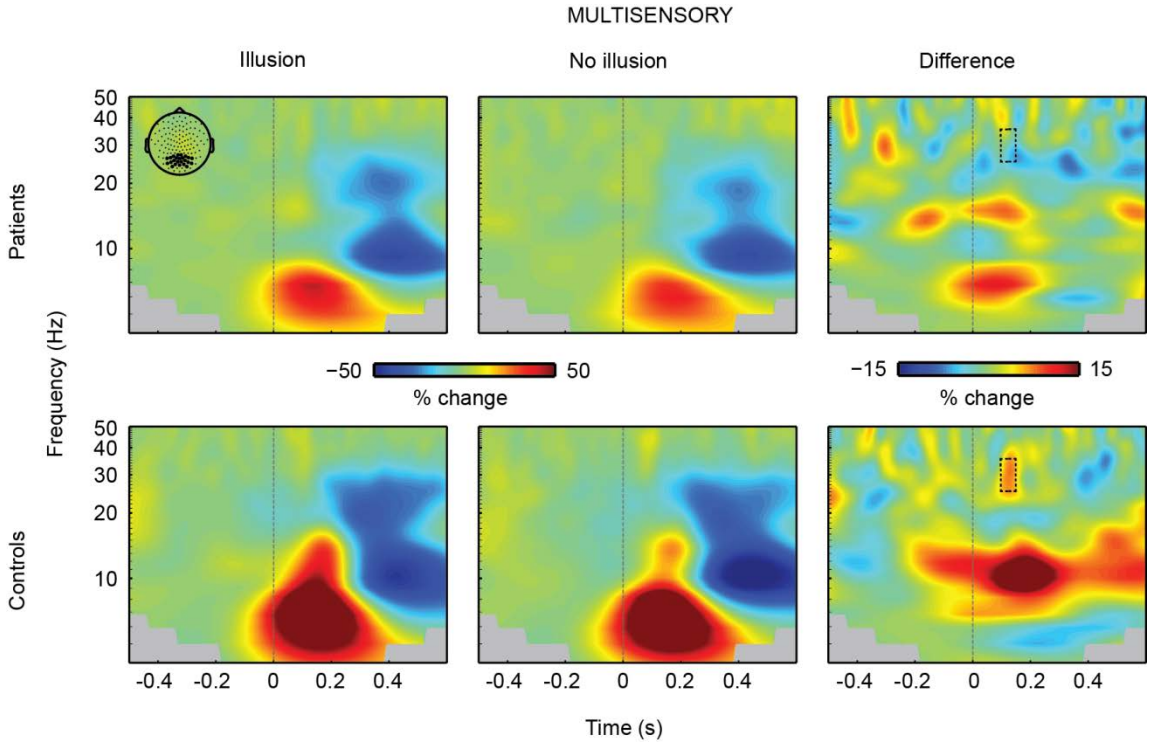

Figure 10: Total oscillatory power over occipital cortex. (A) TFRs at occipital electrodes in response to the critical multisensory A_2V_1 trials. In the early time-frequency window (100–150 ms, 25–35 Hz; highlighted in a box) oscillatory response patterns accompanying illusion and no-illusion trials were different between groups. In the control group, the 25–35 Hz total power was stronger in illusion compared to no-illusion trials. No such difference was found in SCZ. No effects were found in the late time-frequency window (200–240 ms, 25–35 Hz). No Group differences (i.e., SCZ vs. HC) or Group by Condition interactions were found. Time-point 0 indicates the onset of the first auditory and first visual stimulus.

Relevance of the results:

Contrary to my hypothesis, I did not find behavioral differences in the illusion rates between SCZ and HC which can be a sign for compensatory mechanisms in SCZ. However, I found differences in the processing of multisensory stimuli that were visible in the ERPs and in the beta/gamma oscillatory activity (**Figure 11**). My findings are in agreement with ERP studies that suggested aberrant multisensory processing in SCZ (Stekelenburg et al., 2013). Further studies are necessary to examine the associations between altered multisensory processing

and behavioral as well as perceptual outcome in SCZ patients. Additionally, my results confirm previous observations of aberrant oscillatory activity and expand those observations by giving insight into altered sensory processing in SCZ with a multisensory paradigm. Dysfunctional neural oscillations can signify aberrant sensory processing in SCZ. My findings suggest that SCZ compared to HC do process multisensory information differently on a neurophysiological level, even though it can result in the same percept. This furthermore suggests that aberrant multisensory processing is not necessarily linked to altered multisensory perception.

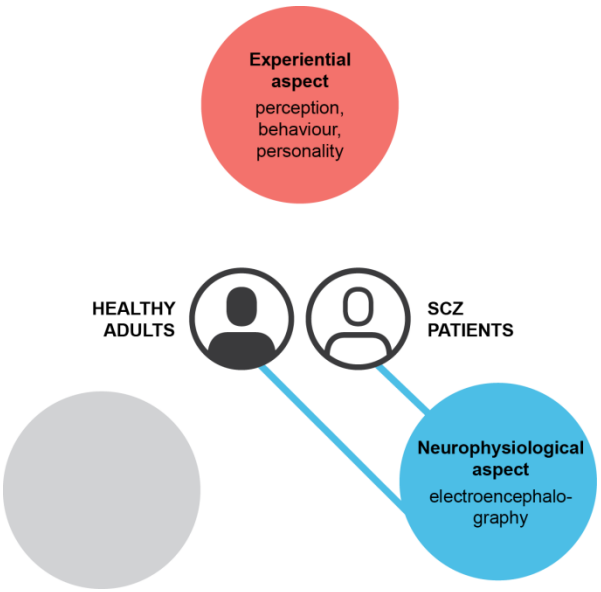

Figure 11: Finding of study 2. I did not observe any correlation between SIFI illusion rates (red circle) and neurophysiological data (blue circle). However, my results suggest differences in the ERPs and TFRs between SCZ patients and HC (blue circle).

5.1 Are varying neurotransmitter concentrations behaviorally relevant for multisensory processing in SCZ?

The results in **Chapter 5** indicate that there are aberrations in the processing of multisensory stimuli in SCZ on a neurophysiological level, whereas I did not find any behavioral differences between SCZ and HC regarding the SIFI illusion rates. It is possible that compensatory mechanisms are responsible for the lack of behavioral differences. SIFI illusion rates could be influenced by the neurotransmitter GABA. In healthy participants I had tested the influence of GABA concentrations on the SIFI illusion rate and found a significant relationship between STS GABA concentrations and behavioral outcome (**study 1**). It was therefore of interest to examine in SCZ patients if the SIFI illusion rate could be mediated by GABA concentrations.

Postmortem studies indicate that SCZ is related to abnormal GABA concentration, e.g. in the hippocampus (Benes et al., 2007; Gonzalez-Burgos, Fish, & Lewis, 2011). I examined GABA concentrations in the main multisensory area STS in a SCZ group and a HC group and correlated the neurotransmitter concentrations with the SIFI illusion rate. Additionally, I tested if GABA concentrations in SCZ differed from GABA concentrations in HC by using an independent samples t-test. I evaluated the data of 19 SCZ patients and 21 matched healthy control participants. My main goal was to find out if there is a link between SIFI illusion rates and GABA concentrations in SCZ. Furthermore, I wanted to know if there are differences in the GABA or glutamate concentrations between SCZ and HC.

Contrary to the results of **study 1** that I conducted with healthy individuals, the results in this analysis with SCZ patients did not reveal a correlation between the SIFI illusion rate and

GABA concentrations in the STS (r(15) = -.293, p = .254) (n = 17). Hence, in SCZ my results do not suggest a mediating influence of GABA concentrations to multisensory processing. Furthermore, GABA concentrations in the STS were not significantly different between SCZ and HC (SCZ: *M* = 1.570, *SD* = 3.800 (n = 17) vs. HC: *M* = 1.428, *SD* = 3.066, t(33) = 1.220, p = .231 (n=18)). However, it needs to be taken into consideration that further studies with larger sample sizes could improve the statistical power in order to find out if STS GABA concentrations of SCZ differ in those from HC. These findings were not submitted for publication.

Where I did not find differences between GABA concentrations in SCZ and HC, a number of other studies reported differences in another neurotransmitter, i.e. glutamate, in various regions (Hugdahl et al., 2015; Marsman et al., 2013; Merritt et al., 2016; Poels et al., 2014; Wijtenburg et al., 2015). Moreover, whereas I did not find differences in illusion rates between SCZ and HC, others have reported such differences (Ross et al., 2007). However, it must be kept in mind that personality traits might affect perception (Kirihara et al., 2012), and altered personality traits have also been found in SCZ (e.g., Berenbaum & Fujita, 1994; Boyette et al., 2013; Camisa et al., 2005; Gurrera et al., 2000; Ohi et al., 2016). Therefore, I decided to focus on the interplay between neurotransmitter concentrations and other experiential aspects in SCZ, e.g. personality traits, which will be referred to in the following chapter.

6. Study 3: Do aberrant glutamate concentrations relate to altered personality in SCZ?

Since I assessed not only GABA but also glutamate concentrations in my previous studies, I developed the explorative question whether aberrant glutamate concentrations could be linked to other experiential aspects, like personality differences in SCZ (see manuscript no. 3, Balz et al., submitted, **Appendix C**).

Research questions and method:

Researchers have been exploring the complexities of glutamatergic neurotransmission since the early 1990s: The glutamate hypothesis posits that there are aberrations in glutamatergic pathways and at glutamate receptors (Chavez-Noriega, Schaffhauser, & Campbell, 2002; Coyle, 1996, 2006; Javitt & Zukin, 1991; Javitt, 2010; Kantrowitz & Javitt, 2010; Poels et al., 2014; Treen et al., 2016). Glutamate receptor dysfunction could lead to dopaminergic alterations, disturbing the complex interactions between glutamatergic, dopaminergic and GABAergic mechanisms (Schwartz, Sachdeva, & Stahl, 2012; Treen et al., 2016). Dopaminergic alterations in SCZ could therefore be mediated by abnormalities in glutamatergic neurotransmission (Laruelle, Kegeles, & Abi-Dargham, 2003; Treen et al., 2016). Insights into the relationship between glutamate neurotransmitters with experiential aspects of schizophrenia would provide a better understanding of the impaired processes in this disorder. Some studies with SCZ patients have indicated altered glutamatergic neurotransmission in the temporal lobe, an area which likely relates to the manifestation of personality traits (Atagün et al., 2015; Li et al., 2017) and in the OCC (Thakkar et al., 2017). Furthermore, studies investigating the Big Five personality traits in SCZ have shown enhanced neuroticism and diminished extraversion scores in SCZ (Berenbaum & Fujita,

1994; Boyette et al., 2013; Camisa et al., 2005; Gurrera et al., 2000; Ohi et al., 2016). Hence, alterations in the glutamatergic system in the STS might relate to altered personality traits in SCZ (**Figure 12**).

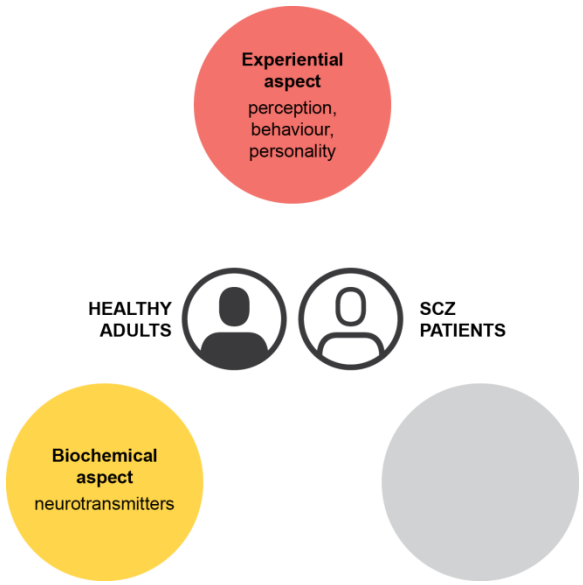

Figure 12: Research question of study 3. The study focused on the interplay between personality traits (red circle) and glutamate concentrations (yellow circle) in SCZ patients compared to HC.

I developed the following exploratory research question:

Are glutamate concentrations altered in SCZ and do they correlate with the personality traits neuroticism and extraversion?

Working hypotheses:

- I expected differences in glutamate concentrations between SCZ and HC (Atagün et al., 2015; Li et al., 2017) (Atagün et al., 2015; Li et al., 2017).
- I assumed that there are personality differences in SCZ, i.e. higher neuroticism scores and lower extraversion scores compared to HC (Berenbaum & Fujita, 1994; Boyette et al., 2013; Camisa et al., 2005; Gurrera et al., 2000; Ohi et al., 2016)

- I hypothesized that differences in glutamate concentrations are linked to alterations in personality of SCZ.

In this study, I examined the relationship between glutamate concentrations in 19 SCZ patients and 21 HC in two VOI encompassing the left STS and the OCC (MRS method details, see **chapter 3.3**), and personality traits. Personality dimensions neuroticism, extraversion, openness, agreeableness and conscientiousness were assessed using the NEO-FFI questionnaire.

Main Results:

SCZ compared to HC showed significantly higher glutamate concentrations in the STS, but not in the OCC (**Figure 13A**). Furthermore, according to my hypothesis, SCZ revealed higher neuroticism scores and lower extraversion scores than HC (**Figure 13B**).

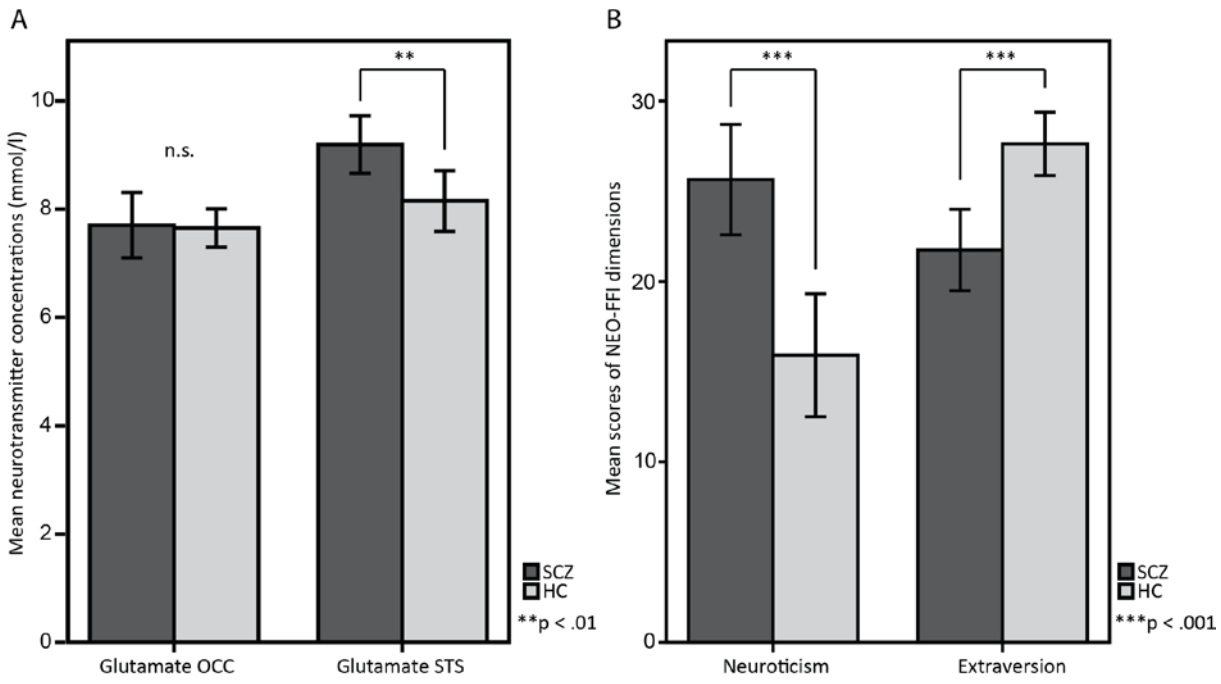

Figure 13: t-tests between SCZ and HC for A) glutamate in the OCC and glutamate in the STS, and for B) the NEO-FFI dimensions neuroticism and extraversion. A) The barplots show OCC and STS mean

glutamate concentrations in SCZ and HC. Glutamate concentrations in the STS are elevated in SCZ compared to HC, whereas OCC glutamate concentrations do not show any differences. B) The barplots show differences between SCZ and HC in the personality dimensions neuroticism and extraversion, measured by the NEO-FFI.

Within SCZ, I found a negative correlation between glutamate concentrations in the STS and neuroticism scores (r(17) = -.537, p = .018), i.e. the higher the glutamate concentrations, the lower neuroticism scores and vice versa. However, this was not found in HC (r(19) = .011, p = .962) (**Figure 14**).

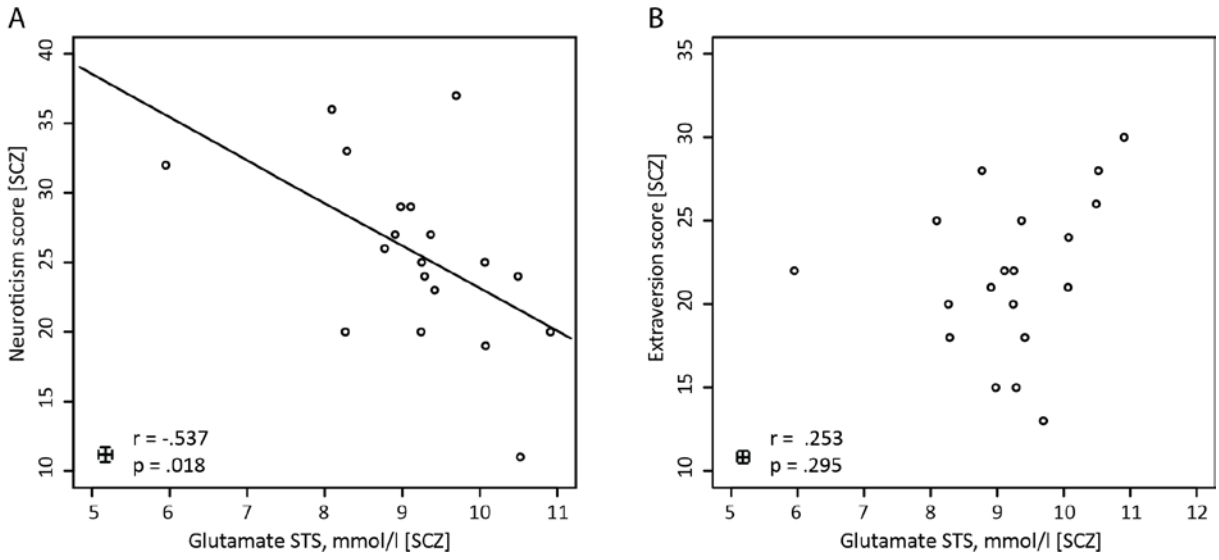

Figure 14: Pearson correlations for SCZ between glutamate (STS) and neuroticism, and between glutamate (STS) and extraversion. A) In SCZ glutamate concentrations in the STS are negatively correlated with neuroticism (n=19). B) In SCZ glutamate concentrations in the STS do not show any correlations with the NEO-FFI extraversion score (n = 19).

Relevance of the results:

The findings of this study revealed that in SCZ, but not in HC, there is an inverse relationship between glutamate concentrations in the STS and alterations in personality traits, as reflected by the neuroticism score (**Figure 15**). I speculate that elevated glutamate

in the STS might serve as a compensatory mechanism that enables patients with enhanced glutamate concentrations to control and prevent the expression of neuroticism. My results could be relevant in studies of psychopharmacological treatment of SCZ, in order to find out how to normalize aberrant glutamatergic neurotransmission. Drugs that target the glutamatergic system could help individuals with SCZ who do not respond to standard medication. Considering that modulations in neurotransmission also affect personality in SCZ, monitoring and moderating the glutamatergic concentration might help to further understand SCZ psychopathology.

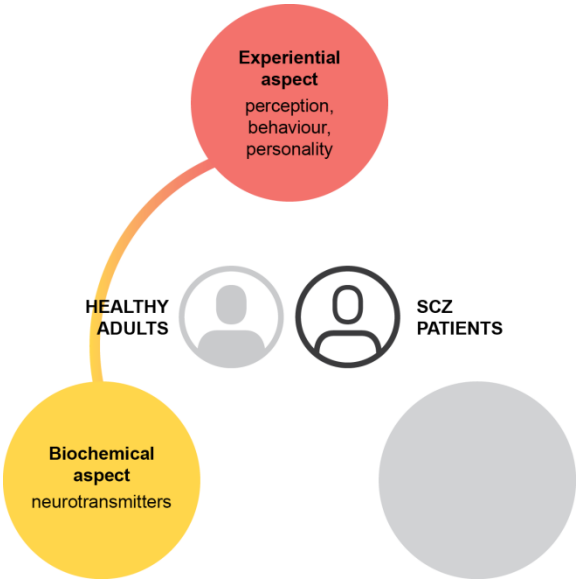

Figure 15: Finding of study 3. In SCZ patients, I observed a negative correlation between the personality dimension neuroticism (red circle) and glutamate concentrations in the STS (yellow circle). This correlation was absent in the HC group.

7. General discussion and outlook

The present work dealt with the interplay between experiential, neurophysiological and biochemical aspects in healthy adults and patients with schizophrenia to get a better insight into the complex interactions that happen in the human brain. To examine this interplay I conducted one study in healthy adults about the relationship between the multisensory SIFI illusion rate, high-frequency oscillations and GABA concentrations in the STS (**study 1**). Furthermore, I examined if SCZ patients differ in any of these aspects from HC or if they show the same relationship between those three measures. Therefore I first examined multisensory processing in SCZ patients and analyzed their ERPs and high frequency oscillations (**study 2**). Since I did not find any relationship between the SIFI illusion rate and oscillatory responses or GABA concentrations, I assessed whether there are other experiential aspects that could relate to aberrant neurotransmitter concentrations in SCZ (**study 3**).

My studies revealed several new findings:

(1) It could be shown for the first time that there is a ***robust three-fold relationship between multisensory processing, gamma oscillations and GABA concentrations in the STS in healthy individuals*** (**study 1**). GABA concentrations mediate the positive relationships between GBO power and audiovisual perception. Thus, my findings confirm that there are relationships between high-frequency oscillations and sensory processing not only in unisensory, but also in multisensory processing (Arnal et al., 2011; Schneider et al., 2011; Senkowski et al., 2005, 2011). The finding that GBO power in the left STS is correlated with the illusion rate is evidence for the role of GBO in audiovisual perception. Differences in the

processing of stimuli in the left STS might contribute to individual differences in audiovisual perception. The strong positive relationship between GABA concentration and GBO power in STS shows that the GABA system could have a modulatory influence on GBO power. Furthermore, the finding that the GABA level in the STS predicts individual differences in audiovisual perception suggests that the GABA system plays a crucial role in multisensory integration. To fully understand the complexity of the human brain it is therefore advisable to work interdisciplinary with research groups from different research fields in neuroscience to gain better insight about the basic processes that happen inside the brain. A question that remains open is that in my studies I measured individual variability in neurotransmitter concentrations as obtained by the MRS. These differences could be attributable to several different parameters, like the differences in the amount of neurons, the synapses, or concentration per neuron. It is not known how these parameters relate to multisensory perception. Furthermore, it is still unsure whether the glutamate system contributes to individual differences in audiovisual perception. Future studies could therefore try to examine if there is a link between glutamate and multisensory perception.

(2) The findings suggest that ***SCZ patients differ in their neurophysiological responses to multisensory stimuli, however, those alterations do not necessarily show in their behavioral responses*** (**study 2**). In comparison to HC, SCZ showed reduced ERP amplitudes in early ERP components of multisensory SIFI trials. In HC larger amplitudes were present irrespective of whether the trials produced an illusion or no-illusion percept which indicates that there were general group differences in the processing of multisensory stimuli between SCZ and HC that are not due to differences in the EEG data quality. I observed differences in multisensory integration effects between groups, however they did not influence the perceptual outcome. This missing behavioral effect in SCZ could be due to

a compensatory mechanism. Interestingly, the absence of behavioral differences between groups has also been shown in other multisensory integration studies (Roa Romero et al., 2016; Stekelenburg et al., 2013) Recently, Bizley et al. (2016) suggested that there are different stages of multisensory integration that occur partly independent from each other. Thus, in SCZ there could be later perception mechanisms that compensates for earlier alterations by addressing additional brain networks (Rentrop et al., 2011). However, this assumption requires further empirical testing, for instance by applying transcranial magnetic stimulation (TMS) at early and late time intervals during the SIFI paradigm. In the case of compensatory mechanisms, TMS that is applied at late time intervals could affect perception in SCZ. The analysis of TFRs showed an enhanced 25-35 Hz power to audiovisual illusion trials in HC, whereas in SCZ there was no enhancement of occipital oscillatory activity in illusion trials, and no power differences between illusion and no-illusion trials.

(3) For the research on the perception and processing of multisensory stimuli, this work generated new insights concerning the significance of the basic audiovisual SIFI paradigm (**studies 1 and 2**). The illusion was induced in about half of the SIFI trials in both SCZ and HC with no differences (comparable illusion rates) between the groups. In unisensory paradigms, aberrances in neural processing often go along with altered perception, which is reflected in behavioral differences (Senkowski & Gallinat, 2015; Uhlhaas & Singer, 2015). Knowing that SCZ differ from HC in the processing and integration of unisensory stimuli, it would have been possible that differences in multisensory processing in the SIFI could lead to different perception rates in SCZ compared to HC. One possible outcome of this could be an increased illusion rate in SCZ compared to HC, because SCZ integrate information more readily than HC by combining stimuli that do not belong together (Lariviere et al., 2017;

Uhlhaas et al., 2006). An alternative outcome of this could be a reduced illusion rate in SCZ, compared to HC by separating stimuli that are normally processed holistically (Keane, Joseph, & Silverstein, 2014). However, it is possible that SCZ compared to HC do have different multisensory processing patterns which could still result in the same perceptual outcome (Sanders et al., 2012). This would be a sign of a compensatory mechanism. Deriving from the behavioral results, in the SIFI paradigm SCZs may not integrate more or less than healthy participants. However, we need to take into account that the perception of an illusion is not a sign of a disturbed process, it merely shows to which extend an individual person integrates signals that derive from different senses. My results suggest that SCZ do show aberrations in the multisensory integration processes at the neural level, but that they are apparently able to compensate for those differences (**study 2**).

(4) My results suggested that there is an ***inverse relationship between STS glutamate concentrations and neuroticism in SCZ*** (**study 3**) which shows that there might be a link between personality as another experiential aspect and biochemical processes in SCZ. It is interesting that SCZ showed overall higher neuroticism scores and higher glutamate concentrations in the STS than HC, and that within SCZ glutamate concentrations in the STS correlated negatively with neuroticism scores. SCZ might be able to compensate for the expression of neuroticism traits by higher glutamate concentrations. Future research could examine the predictive value of enhanced neuroticism scores for the development of SCZ. This finding shows again that several aspects of processes in the brain depend on each other and that it could be an advantage to combine several methods when trying to further the understanding of basic principles about the brain.

In general, this work aimed to further the understanding of basic neural processes and the interplay between oscillatory, glutamatergic processes modulating information transfer in the brains of healthy adults, as well as potential dysfunction in these processes in SCZ. To do this, I examined multisensory processing, perception, personality and neurophysiological and biochemical differences between the groups. For future studies it would be of particular interest for the field of multisensory research, if the three-fold relationship between SIFI illusion rate, GBO oscillations and STS GABA concentrations could be replicated in a SCZ patients group. I predict that the statistical power might not have been strong enough, since I analyzed data of 39 healthy participants in the first study, but measured 24 SCZ patients for the second and third study, and of some of them it was not possible to obtain valid neurotransmitter values to compare against HC. It also needs to be considered that my study sample consisted of overall high-functioning patients who were not in an acute psychotic phase and therefore did not show severe positive symptoms. This might also be a reason why we did not find any differences between SCZ and HC in the PANSS nor the BACS scores. However, it would have been very difficult to measure SCZ in their acute psychotic phases, because they would very likely not have been able to stay focused throughout the measurements. This would have severely influenced data quality and the behavioral results. Although we tested the influence of medication on our results in **studies 2 and 3**, its effects are complex, and the different medications could also have played a role in the low effect size. I therefore suggest that it is possible that the interaction between multisensory processing, neutrotransmitter concentrations and oscillatory activity in SCZ functions in another way than in healthy participants, as such that compensatory mechanisms during the processing of stimuli lead to the same behavioral result compared to healthy adults. However, this speculation requires further testing. It certainly would be interesting to further

investigate, whether the threefold relationship between experiential aspects, neurophysiology and neurochemistry can also be found in SCZ patients. Further studies of the relationship between the three aspects could also manipulate one of the aspects and then acquire the influences on the other two aspects or it would be possible to monitor for example the relationship between glutamate concentrations and personality factors over time to find clues about their stability. However, for this longitudinal study designs would be necessary.

The overall results of this work contribute to the basic research about neurophysiological and biochemical processes and their interplay with aspects related to behavior, perception and personality in healthy adults and SCZ in the association cortex and has practical implications for the development of treatment options for individuals with schizophrenia.

8. Abbreviations

BACS	Brief Assessment of Cognition in Schizophrenia
EEG	electroencephalogram
ERP	event-related potential
GABA	gamma-aminobutyric acid
GBO	gamma band oscillations
HC	healthy control
MRS	magnetic resonance spectroscopy
NEO-FFI	NEO-Five Factory Inventory
OCC	occipital cortex
PANSS	Positive and Negative Syndrome Scale
SCZ	schizophrenia
SIFI	Sound Induced Flash Illusion
STS	superior temporal sulcus
TMS	transcranial magnetic stimulation
TFR	Time–frequency representation

9. References

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10. Curriculum Vitae

For reasons of data protection,

the curriculum vitae

is not included in the published version.

11. List of own publications and conference abstracts

Publications:

Balz, J., Roa Romero, Y., Keil, J., Schubert, F., Ittermann, B., Montag, C., Gallinat, J., & Senkowski, D. (2017). *Glutamate concentration in the superior temporal sulcus relates to neuroticism in schizophrenia.* Manuscript submitted for publication.

Balz, J., Roa Romero, Y., Keil, J., Krebber, M., Niedeggen, M., Gallinat, J., & Senkowski, D. (2016). Beta/Gamma oscillations and event-related potentials indicate aberrant multisensory processing in schizophrenia. *Frontiers in Psychology, 7*, 1-12.

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Roa Romero, Y., Keil, J., **Balz, J.**, Niedeggen, M., Gallinat, J., & Senkowski, D. (2016). Alpha-band oscillations reflect altered multisensory processing oft he McGurk illusion in schizophrenia. *Frontiers in Human Neuroscience, 10*, 1-12.

Balz, J., Keil, J., Roa Romero, Y., Mekle, R., Schubert, F., Aydin, S., Ittermann, B., Gallinat, J. & Senkowski, D. (2016). GABA concentration in superior temporal sulcus predicts gamma power and perception in the sound-induced flash illusion. *NeuroImage, 125*, 724-730.

Conference Abstracts:

Balz, J., Roa Romero, Y., Keil, J., Schubert, F., Mekle, R., Ittermann, B., Montag, C., Gallinat, J., Senkowski, D. (2016). *Elevated glutamate concentration in the superior temporal sulcus relates to altered neuroticism in schizophrenia.* Poster presented at the DGPPN: Annual Congress of the German Association for Psychiatry and Psychotherapy, Berlin, Germany.

Balz, J., Roa Romero, Y., Keil, J., Schubert, F., Mekle, R., Ittermann, B., Montag, C., Gallinat, J., Senkowski, D. (2016). *Glutamate concentration in the superior temporal gyrus is linked to neuroticism in schizophrenia.* Poster presented at the DGPs: 42. Tagung Psychologie & Gehirn 2016, Berlin, Germany.

Balz, J., Roa Romero, Y., Keil, J., Krebber, M., Pomper, U., Gallinat, J., Senkowski, D. (2014). *Altered evoked gamma band oscillations during multisensory processing of the sound-induced flash illusion in schizophrenia.* Poster presented at the IMRF 2015: 16th International Multisensory Research Forum, Pisa, Italy.

Balz, J., Roa Romero, Y., Keil, J., Krebber, M., Pomper, U., Gallinat, J., Senkowski, D. (2014). *Altered neural activity during the sound induced flash illusion in schizophrenia*. Poster presented at the SfN 2014 Annual Meeting: Society for Neuroscience, Washington, D.C..

Balz, J., Roa Romero, Y., Keil, J., Pomper, U., Gallinat, J., Senkowski, D. (2014). *Event-related neural activity during multisensory processing in schizophrenia.* Poster

presented at the OHBM 2014 Annual Meeting: Organization for Human Brain Mapping, Hamburg, Germany.

Balz, J., Roa Romero, Y., Keil, J., Pomper, U., Gallinat, J., Senkowski, D. (2014). *Neurophysiological markers of multisensory processing in schizophrenia*. Poster presented at the ICCN 2014: 30th International Congress of Clinical Neurophysiology of the IFCN, Berlin, Germany.

Balz, J., Roa Romero, Y., Keil, J., Pomper, U., Gallinat, J., Senkowski, D. (2013). *Multisensory processing during the sound induced flash illusion in schizophrenia*. Poster presented at the DGPPN: Annual Congress of the German Association for Psychiatry and Psychotherapy, Berlin, Germany.

Balz, J., Roa Romero, Y., Keil, J., Pomper, U., Gallinat, J., Senkowski, D. (2013). *Multisensory Integration in Schizophrenia: Preliminary Findings and Outlook.* Poster presented at the 12th Charité Conference on Psychiatric Research: Emotional Neuroscience, Berlin, Germany.

12. Appendices A-C: Original publications

My dissertation is based on the following publications:

A: Balz, J., Keil, J., Roa Romero, Y., Mekle, R., Schubert, F., Aydin, S., Ittermann, B., Gallinat, J. & Senkowski, D. (2016). GABA concentration in superior temporal sulcus predicts gamma power and perception in the sound-induced flash illusion. *NeuroImage, 125*, 724-730. https://doi.org/10.1016/j.neuroimage.2015.10.087

B: Balz, J., Roa Romero, Y., Keil, J., Krebber, M., Niedeggen, M., Gallinat, J., & Senkowski, D. (2016). Beta/Gamma oscillations and event-related potentials indicate aberrant multisensory processing in schizophrenia. *Frontiers in Psychology, 7*, 1-12. https://doi.org/10.3389/fpsyg.2016.01896

C: Balz, J., Roa Romero, Y., Keil, J., Schubert, F., Ittermann, B., Montag, C., Gallinat, J., & Senkowski, D. (2018). Glutamate concentration in the superior temporal sulcus relates to neuroticism in schizophrenia. Meanwhile published in *Frontiers in Psychology, 9*, 578. https://doi.org/10.3389/fpsyg.2018.00578

Eidesstattliche Erklärung

Eidesstattliche Erklärung nach § 7 Abs. 4 der Promotionsordnung zum Dr. rer. nat. / Ph. D. des Fachbereichs Erziehungswissenschaft und Psychologie der Freien Universität Berlin vom 08. August 2016:

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne die unzulässige Hilfe Dritter verfasst und nur die angegebenen Quellen und Hilfsmittel benutzt habe. Des Weiteren erkläre ich, dass die Dissertation weder in Teilen noch in ihrer Gesamtheit einer anderen wissenschaftlichen Hochschule zur Begutachtung in einem Promotionsverfahren vorliegt oder vorgelegen hat.

_____ _____

Ort, Datum Dipl.-Psych. Johanna Balz

Erklärung gemäß § 7 Abs. 3 Satz 4 der Promotionsordnung über den Eigenanteil an den veröffentlichten oder zur Veröffentlichung vorgesehenen eingereichten wissenschaftlichen Schriften im Rahmen meiner publikationsbasierten Arbeit

I. Name, Vorname: Balz, Johanna

Institut: Fachbereich Erziehungswissenschaft und Psychologie der Freien Universität Berlin

Promotionsfach: Psychologie

Titel: Dr. rer. nat.

II. Nummerierte Aufstellung der eingereichten Schriften:

1. Balz, J., Keil, J., Roa Romero, Y., Mekle, R., Schubert, F., Aydin, S., Ittermann, B., Gallinat, J. & Senkowski, D. (2016). GABA concentration in superior temporal sulcus predicts gamma power and perception in the sound-induced flash illusion. *NeuroImage, 125*, 724-730.

2. Balz, J., Roa Romero, Y., Keil, J., Krebber, M., Niedeggen, M., Gallinat, J., & Senkowski, D. (2016). Beta/Gamma oscillations and event-related potentials indicate aberrant multisensory processing in schizophrenia. *Frontiers in Psychology, 7*, 1-12.

3. Balz, J., Roa Romero, Y., Keil, J., Schubert, F., Ittermann, B., Montag, C., Gallinat, J., & Senkowski, D. (2017). *Glutamate concentration in the superior temporal sulcus relates to neuroticism in schizophrenia.* Manuskript am 24.10.2017 eingereicht bei bei *Frontiers in Psychiatry*.

III. Darlegung des eigenen Anteils an diesen Schriften:

zu II. 1.:

- Entwicklung der Konzeption (in Teilen)
- Planung, Vorbereitung und Organisation des Experiments (mehrheitlich)
- Literaturrecherche (überwiegend)
- Versuchsdesign (mehrheitlich)
- Probandenrekrutierung (mehrheitlich)
- Datenerhebung der Verhaltens- und neurophysiologischen Daten (mehrheitlich)
- EEG-Datenvorverarbeitung (vollständig) und statistische Analyse (mehrheitlich)
- Ergebnisdiskussion (mehrheitlich)
- Anfertigen des Manuskripts (mehrheitlich)
- Einreichung und Überarbeitung des Manuskripts (überwiegend)

zu II. 2.:

- Entwicklung der Konzeption (überwiegend)
- Planung, Vorbereitung und Organisation des Experiments (mehrheitlich)
- Literaturrecherche (überwiegend)
- Versuchsdesign (mehrheitlich)
- Probandenrekrutierung (mehrheitlich)
- Datenerhebung der Verhaltens- und neurophysiologischen Daten (mehrheitlich)
- EEG-Datenvorverarbeitung (vollständig) und statistische Analyse (überwiegend)
- Ergebnisdiskussion (mehrheitlich)
- Anfertigen des Manuskripts (mehrheitlich)

- Einreichung und Überarbeitung des Manuskripts (überwiegend)

zu II. 3.:

- Entwicklung der Konzeption (überwiegend)
- Planung, Vorbereitung und Organisation des Experiments (mehrheitlich)
- Literaturrecherche (vollständig)
- Versuchsdesign (mehrheitlich)
- Probandenrekrutierung (mehrheitlich)
- Datenerhebung der Verhaltensdaten (mehrheitlich)
- Statistische Analyse (überwiegend)
- Ergebnisdiskussion (überwiegend)
- Anfertigen des Manuskripts (überwiegend)
- Einreichung des Manuskripts (vollständig)

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Datum, Unterschrift der Doktorandin

Ich bestätige die von Johanna Balz unter III. abgegebene Erklärung:

Name: Unterschrift: . . . . . .

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