Aus der Klinik für Psychiatrie und Psychotherapie
Geschäftsführender Direktor: Prof. Dr. Tilo Kircher

des Fachbereichs Medizin der Philipps-Universität Marburg

# Neural basis of speech-gesture mismatch detection in schizophrenia spectrum disorders

Inaugural-Dissertation zur Erlangung des Doktorgrades der gesamten Humanmedizin

dem Fachbereich Medizin der Philipps-Universität Marburg
vorgelegt von

Momoko Choudhury aus Frankfurt am Main

Marburg, 2023

Angenommen vom Fachbereich Medizin der Philipps-Universität Marburg am 22.06.2023

Gedruckt mit Genehmigung des Fachbereichs Medizin

Dekanin: Prof. Dr. Denise Hilfiker-Kleiner
Referent: Prof. Dr. Benjamin Straube
1. Korreferent: Prof. Dr. Carsten Möller

# Table of contents

Table of contents....3
List of abbreviations....6
List of figures....8
List of tables....9
1. Introduction....10
2. Background....12
  2.1. Schizophrenia and Schizophrenia Spectrum Disorders....12
  2.2. Speech processing....16
  2.3. Speech perception in schizophrenia spectrum disorders....19
    2.3.1. Speech processing in patients with SSD....19
    2.3.2. Abstract language....21
  2.4. Neural processing of gestures....23
  2.5. Gesture deficits in schizophrenia spectrum disorders....27
  2.6. Speech-gesture mismatch detection....30
  2.7. Aims of the study....32
  2.8. Hypotheses....34
3. Methods....35
  3.1. Study sample....35
    3.1.1. Patients....35
    3.1.2. Healthy Control Group....36
  3.2. Stimuli....38
  3.3. Functional magnetic resonance imaging....40
  3.4. Experimental design....42
  3.5. fMRI data acquisition....43
  3.6. Data analysis....43
    3.6.1. Behavioral data analysis (Part A)....43
    3.6.2. fMRI data analysis (Parts B and C)....44
      3.6.2.1 Group analysis....45
      3.6.2.2 Contrasts of interest....46
        3.6.2.2.1. Part B....46
        3.6.2.2.2. Part C....46
4. Results....48
  4.1. Part A (Behavioral data)....48

4.1.1. Detection rates....48
4.1.2. Hit rates and False alarm rates....48
4.1.3. Response criterion....48
4.2. Part B: fMRI data (relatedness)....51
4.3. Part C: fMRI data (abstractness)....54
5. Discussion....57
5.1. Part A: Behavioral data....57
5.1.1. Detection rates, hit rates and false alarm rates....57
5.1.2. Response criterion....60
5.2. Part B: Relatedness....61
5.2.1. The SMA and motor cortex contributions to speech and gesture processing…61
5.2.2. The ACC - dysfunctional conflict processing?....62
5.2.3. Frontotemporal hyperactivation....63
5.3. Part C: Abstractness....65
5.3.1. The role of the IFG in speech and gesture....66
5.3.2. Temporal lobe integrity in SSD....68
5.4. Limitations....70
5.5. Implications and outlook....71
5.6. Conclusion....74
6. Summaries....75
6.1. Summary (English)....75
6.2. Zusammenfassung (deutsch)....77
7. References....80
8. Appendix....111
8.1. Supplementary results tables....111
8.2. Study material....115
8.2.1. MRI properties....115
8.2.2. Design Matrix....116
8.2.3. Monte-Carlo-Simulation....117
8.2.4. Declaration of informed consent....118
8.2.5. Data privacy statement....120
8.2.6. Sociodemographic questionnaire....123
8.2.7. Follow-up questionnaire....124
8.2.8. Multiple-Choice Word Test B (Lehrl et al., 1995)....126
8.2.9. Scale for Assessment of Positive Symptoms (N. Andreasen, 1984b) and Scale for Assessment of Negative Symptoms (N. Andreasen, 1984a)....128

8.3. Index of academic teachers........................................................................136
8.4. Acknowledgements...................................................................................137

# List of abbreviations

| | |
|---|---|
| AAL | Automated Anatomical Labelling |
| abs | abstract |
| ACC | anterior cingulate cortex |
| ANOVA | Analysis of Variance |
| AR or abs/rel | abstract related |
| AU or abs/unr | abstract unrelated |
| BOLD | blood-oxygen level dependency |
| c | response criterion |
| C | controls |
| CI | confidence interval |
| con | concrete |
| CPZ | Chlorpromazine |
| CR or con/rel | concrete related |
| CU or con/unr | concrete unrelated |
| d' | detection rate |
| deg | degrees |
| DGPPN | Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde |
| DIM | dimensions |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EEG | electroencephalography |
| e.g. | exempli gratia |
| EPI | echo-planar imaging |
| ERP | event-related brain potentials |
| F | False alarm rate |
| Fig. | Figure |
| FTD | Formal thought disorder |
| fMRI | functional magnetic resonance imaging |
| FoV | field of view |
| FWHM | Full width at half maximum |
| H | Hit rate |
| rel | related |
| rm-ANOVA | repeated-measures ANOVA |
| ROL | rolandic operculum |
| RRID | Research Resource Identifiers |
| HRF | hemodynamic response function |
| ICD | International Classification of Diseases |
| i.e. | Id est |
| IFG | inferior frontal gyrus |
| IPL | inferior parietal lobule |
| ITG | inferior temporal gyrus |
| ITS | inferior temporal sulcus |
| L | left |
| MEG | magnetoencephalography |
| MAO | monoamino oxidase |
| MCC | middle cingulate cortex |
| mg | milligrams |
| MFG | middle frontal gyrus |
| min | minutes |
| mm | millimeters |
| mm$^2$ | square millimeters |
| MNI | Montreal Neurological Institute |
| MOG | middle occipital gyrus |
| MRI | magnetic resonance imaging |
| ms | milliseconds |
| MSFG | medial segment of superior frontal gyrus |
| MTG | middle temporal gyrus |
| MWT-B | Multiple-Choice Word Test B |
| n/N | number of participants |
| P | patients |
| PANSS | Positive and Negative Syndrome Scale |
| PCC | posterior cingulate cortex |
| PrG | precentral gyrus |
| R | right |
| RDoC | Research Domain Criteria |
| z | z score |

| | |
|---|---|
| rTMS | repetitive transcranial magnetic stimulation |
| s | seconds |
| SANS | Scale for Assessment of Negative Symptoms |
| SAPS | Scale for Assessment of Positive Symptoms |
| SD | Standard Deviation |
| SFG | superior frontal gyrus |
| SMA | supplementary motor area |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SOG | superior occipital gyrus |
| SPG | superior parietal gyrus |
| SPM | Statistical Parametric Mapping |
| SPSS | Statistical Package for the Social Sciences |
| Spt | sylvian parietal temporal |
| SSD | Schizophrenia spectrum disorder(s) |
| SSRI | selective serotonin reuptake inhibitor |
| STG | superior temporal gyrus |
| STS | superior temporal sulcus |
| T1 | Longitudinal relaxation time |
| T2 | Transverse relaxation time |
| Tab. | table |
| tDCS | transcranial direct current stimulation |
| TE | echo time |
| TMP | temporal pole of middle temporal gyrus |
| TR | repetition time |
| TSP | temporal pole of superior temporal gyrus |
| TULIA | Test of upper limb apraxia |
| unr | unrelated |
| VOI | volumes of interest |
| WFU | Wake Forest Universitiy |
| YLD | years lived with disability |

# List of figures

Figure 1: Speech processing........................................................................................17
Figure 2: Speech processing in SSD patients.......................................................................19
Figure 3: The semantic unification theory (Hagoort et al., 2009; Willems et al., 2009) according to Straube et al., 2011, modified and simplified..................................................26
Figure 4: Video conditions..........................................................................................39
Figure 5: Detection rates, hit rates and false alarm rates....................................................49
Figure 6: Activation patterns for unrelated > related stimuli.................................................52
Figure 7: Activation patterns for abstract > concrete stimuli.................................................55

Supplementary Figure 1: MRI properties.........................................................................115
Supplementary Figure 2: Design Matrix in SPM12 (Flexible-factorial analysis)..................116
Supplementary Figure 3: Monte-Carlo-Simulation for minimal voxel contiguity threshold (Slotnick, 2017; Slotnick et al., 2003)..................................................................117

# List of tables

Table 1 Diagnostic criteria of F20, following ICD-10 (DGPPN e.V. 2019)............................13
Table 2: Sociodemographic characteristics...........................................................................37
Table 3: Detection rates d’ and response criterion c............................................................50
Table 4: fMRI results for unrelated versus related stimulus processing...............................53
Table 5: fMRI results for abstract > concrete stimulus processing.......................................56

Supplementary Table 1: Neuropsychological battery.........................................................111
Supplementary Table 2: Effects of handedness.................................................................112
Supplementary Table 3: Effects of sex on result clusters...................................................113
Supplementary Table 4: Effects of age...............................................................................114

# 1. Introduction

In daily-life conversations, spoken language naturally coincides with manual gestures. As appropriate use and comprehension of gestures are integral for successful communication, they greatly influence social interaction and life quality. Especially in **schizophrenia spectrum disorders** (SSD), impaired communication can have wide-ranging effects on patients' social functionality and rehabilitation. There is converging evidence for disturbances of imitation, pantomime (Matthews et al., 2013; Walther et al., 2013a, 2013b, 2015; Wüthrich, Pavlidou et al., 2020), recognition (Berndl et al., 1986; Karakuła et al., 2013), and interpretation of gestures in schizophrenia (Bucci et al., 2008; White et al., 2016). In particular, SSD patients have difficulties understanding and processing abstract language, such as metaphors (Kircher et al., 2007; Mossaheb et al., 2014). Gestures which accompany abstract language (e.g., a circular movement with the index finger to indicate repetition) are also differentially processed in SSD (Straube, Green, et al., 2013, 2014). However, the correct understanding and interpretation of abstract information is very important for successful daily-life communication. Deficits in abstractness processing are therefore highly relevant subjects of research. Furthermore, it has been observed that SSD patients show difficulties in correctly assessing the relationship between speech and corresponding gesture (Nagels et al., 2019). The ability to assess whether spoken language and gesture are semantically related or not is an important communicative function. It requires the observer to extract disparate meanings out of two modalities - speech and gesture - and to successfully integrate those on a meta-level. Difficulties in correctly identifying their relation can therefore indicate impairments of speech and gesture processing, perception, and comprehension - all of which are pivotal for communication and **social functioning**. A recent study even showed that neurostimulation can modify patients' assessment performance, a finding that may lay the groundwork for novel therapeutic approaches (Schülke & Straube, 2019). However, the **neural mechanisms** underlying defective speech-gesture mismatch perception are yet unknown.

In the current study, the **speech-gesture mismatch detection paradigm** for **abstract and concrete** semantic contexts was implemented while simultaneously acquiring **functional magnetic resonance imaging** (fMRI) data. This novel approach allowed for an investigation of brain areas associated with impaired mismatch and abstractness processing.

Speech-gesture mismatch and abstractness perception are highly complex in that they involve a plethora of brain functions. This dissertation will give a general overview of SSD, the neural processes involved in speech and gesture perception, and the respective impairments observed in SSD patients, especially in abstract and semantically unrelated contexts, before focussing on the speech-gesture mismatch paradigm. An illustration of the aims and methods of this study will be followed by a demonstration and critical discussion of the results, also in light of emerging brain-stimulation (Schülke & Straube, 2019; Walther et al., 2019) and speech-gesture therapies (Riedl et al., 2020).

# 2. Background

## 2.1. Schizophrenia and Schizophrenia Spectrum Disorders

**Schizophrenia** is a mental health disorder that affects approximately 21 million people around the globe (Charlson et al., 2018). It is most commonly diagnosed in both women and men between ages 15 and 35 (DGPPN e.V., 2019; McGrath et al., 2008) and often has a debilitating effect on patients' lives (Galderisi et al., 2014). Schizophrenia was the 12th most disabling disorder in the Global Burden of Disease Study 2016, accounting for **1.7% of all years lived with disability** (YLD) globally (Charlson et al. 2018). Life expectancy in patients with schizophrenia is 15 years below average (Hjorthøj et al., 2017; Liu et al., 2017). Considering the high individual and socio-economic burden of schizophrenia, neuroscientific research is still needed to understand pathomechanisms and enable earlier diagnosis and adequate treatments.

The schizophrenia spectrum is characterized by **acute psychoses** of episodic nature as well as variably **chronic or remitting psychotic, cognitive and affective symptoms** (DGPPN e.V., 2019). Schizophrenia and other delusional disorders are grouped under F20.X - F29 in the ICD-10 classification. Diagnostic criteria for F20 following ICD-10 are listed in table 1.

For a **diagnosis according to ICD-10**, symptoms must be persistent for at least one month and organic causes, such as intoxications, must be ruled out. Positive symptoms (an "addition" to normal function/perception: delusions, hallucinations, ego-disturbances) are usually more prominent during acute psychotic phases, whereas negative symptoms (a "reduction" of normal functions: alogia, apathy, social withdrawal) tend to persist chronically and thus have a substantial impact on patients' lives (DGPPN e.V., 2019; Galderisi et al., 2018). Disturbances of speech and communication can be categorized as positive symptoms (formal thought disorder, see chapter 2.3.) or negative symptoms (alogia, emotional bluntness) (Mitra et al., 2016). Clinical scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or the Scales for Assessment of Positive

Symptoms (SAPS) (Andreasen, 1984b) and Negative Symptoms (SANS) (Andreasen, 1984a) can be used to measure their manifestation.

Table 1 Diagnostic criteria of F20, following ICD-10 (DGPPN e.V. 2019)

At least one symptom of categories 1-4 or two symptoms of categories 5-8 must be persistent for one month for the diagnosis of schizophrenia

| | |
|---|---|
| 1 | Ego-disturbances (thought withdrawal, thought broadcasting) |
| 2 | Delusion of control, influence or passivity, delusional perception |
| 3 | Hallucinatory voices commenting or discussing about the patient in the third person |
| 4 | Bizarre, culturally inappropriate, or unrealistic delusion |
| 5 | Persistent hallucinations of any modality |
| 6 | Thought blocking or thought insertion affecting the train of thought |
| 7 | Catatonia, agitation, stereotypical postures, negativism, stupor |
| 8 | Negative symptoms: apathy, poverty of speech, blunt or inappropriate affect |

The **DSM-5 classification** is acknowledging the heterogeneity of the illness by dropping the subtypes of schizophrenia (paranoid, hebephrenic, catatonic, etc.) and summarizing related disorders (including schizoaffective disorder, other psychotic disorders) under the term “Schizophrenia Spectrum and Other Psychotic Disorders”, which rather form a continuous scale than single categories (Bhati, 2013). This enables a scientific approach that is centered around specific symptoms and research findings (imaging, genetics, etc.) on scales between normal and abnormal with less constraints by the historical nomenclature, as proposed by the Research Domain Criteria (RDoC) initiative (Walter, 2017).

The **socioeconomic impact** of schizophrenia can be explained by the high rate of disability, comorbidity, and suicide (Charlson et al., 2018; Hjorthøj et al., 2017). Especially persisting negative symptoms and cognitive impairment and long untreated cases are associated with a poor prognosis (Álvarez-Jiménez et al., 2012; Marshall et al., 2005; Murru & Carpiniello, 2018).

The **underlying causes** of schizophrenia spectrum disorders are not yet fully understood. A genetic heritability of 50% has been suggested (Kircher & Gauggel,

2008) and over 200 risk gene loci have been identified so far (Liu et al., 2021; Pardiñas et al., 2018). Social, economic, and biological circumstances add to a multifactorial list of risk factors including birth complication, father's age, history of migration, cannabis abuse, and traumatic life events (DGPPN e.V., 2019; Kircher & Gauggel, 2008). Protective factors, such as coping mechanisms and resilience, can have a positive effect on manifestation and outcome (Bozikas & Parlapani, 2016; Galderisi et al., 2014; Mizuno et al., 2016; Palmer et al., 2014).

On a neural level, discrete structural abnormalities of gray and white matter have been reported (Olabi et al., 2011). Specifically, dysconnectivity of brain circuits may be accountable for cognitive impairment and have thus received much attention with emerging modern imaging methods (Kircher & Gauggel, 2008; Fitzsimmons et al., 2013; Klauser et al., 2017; Nath et al., 2021). Furthermore, the efficacy of dopamine receptor antagonists in the treatment of positive symptoms indicates an imbalance of neurotransmitters, involving dopamine ("hyperdopaminergic syndrome") and glutamate ("hypoglutamatergic condition"), as suggested by genetic and pharmacological studies (Kircher & Gauggel, 2008; Seeman, 2009).

In sum, it can be said that no striking structural or chemical finding is pathognomonic for SSD. Rather, a variety of subtle biological changes can be found in individuals with similar clinical presentation. This is why further fundamental research on brain functions in SSD is highly relevant.

The **treatment of SSD** is based on a multimodal and multi-professional concept and should be individually adapted. Besides pharmacotherapy using antidopaminergic antipsychotics, psychotherapeutic, social, and rehabilitation therapies are vital. Somatic treatments, such as electroconvulsive therapies and transcranial magnetic stimulation can be options for pharmacoresistant symptoms in some cases (DGPPN e.V., 2019)**.** In general, it can be said that positive symptoms are much more receptive to therapy than negative symptoms (Kircher & Gauggel, 2008).

SSD patients often have difficulties in social situations, presumably due to impaired communicative skills (Walther et al., 2015; White et al., 2016). Disturbances of thought and language are especially resistant to the above-mentioned current therapy options (Wüthrich, Pavlidou, et al., 2020). Therefore, further research examining the mechanisms involved in the neural processing of speech and gesture are needed.

Successful speech processing relies on the integrity of a complex neural system (chapter 2.2) that can be disrupted on many levels in SSD patients (chapter 2.3.1). As a consequence, especially abstract language is frequently impaired (chapter 2.3.2). In daily-life communication, speech and language is always intertwined with nonverbal communicative cues, such as gestures - which share a similar neural integration system (chapter 2.4.). However, SSD patients have difficulties in successfully integrating related and unrelated gestural information (chapter 2.5.). A mismatch-detection paradigm that evaluates the ability to integrate gesture and speech has been used in previous studies to understand the impaired neural processes in SSD (chapter 2.6.). In this study, the mismatch-detection paradigm was implemented to investigate abstractness and relatedness processing in SSD.

In the following, a general overview on the steps involved in speech processing will be delivered before focussing on speech-gesture impairments in SSD.

## 2.2. Speech processing

The perception of spoken language relies on a complex neural system. A model by Ellis and Young from 1988 attempts to break down the process of speech perception into interacting systems (Ellis & Young, 2013). The **acoustic analysis system** processes speech sounds into segments and units, analyzes prosody and intensity, in order to find representation in the auditory input lexicon. Then, the information is matched and compared to the mentally available semantic representation in memory (mental lexicon). Multiple representations can be activated and made accessible at this stage (*lexical access*). Subsequently, the most accurate representation is selected (*lexical selection*). Speech production goes one step further and involves the auditive output lexicon and the **phonological system** (Ellis & Young, 2013; Kircher & Gauggel, 2008).

The mental lexicon - or **semantic network** - provides a web of all known semantic and syntactic information. New input is compared to existing representations, which are activated along the network (**spreading activation**), so that the most adequate meaning can be selected. This network, in accordance with a model by Collins and Loftus (1975), consists of semantic units that are interconnected with each other in terms of semantic relatedness. The closer the distance between two units, the closer the conceptual relatedness (e.g., apple - tree). Units can be indirectly related via a mutual relative (e.g., apple - tree - wood), forming a large associative network that facilitates fast access to semantic content. This model is supported by **priming experiments:** a word (target) can be pronounced or recognized faster if it is preceded by a semantically related word (prime) in terms of reaction times (Minzenberg et al., 2002; Neely, 1991).

For successful **comprehension of words and sentences**, contextual, semantic and syntactic information have to be taken into account and integrated (*lexical integration*). The more ambiguous the input (e.g., metaphors, irony, humor), the more contextual and global aspects are needed (Kircher & Gauggel, 2008). Some models suggest a uniquely bottom-up mechanism, where input is accessed independent from higher-order information such as global context. Others support a process where top-down modulation of lexical selection is possible via context-dependent spreading activation (Kircher & Gauggel, 2008).

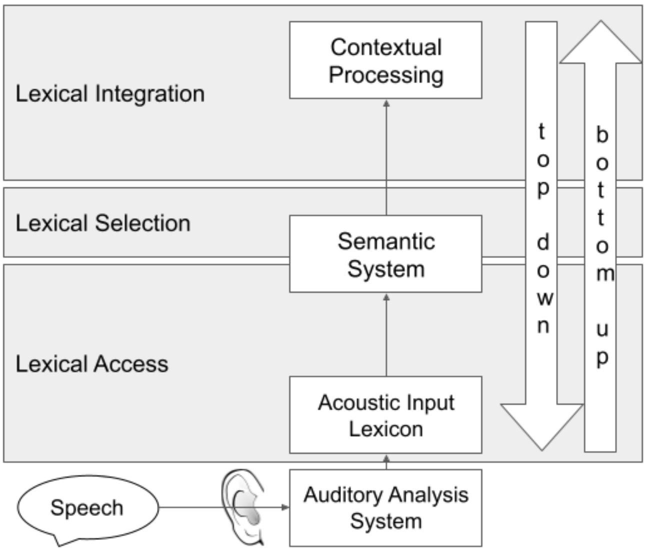


Figure 1: Speech processing
A schematic and simplified illustration of the processes involved in speech perception and comprehension, with elements from Ellis and Young (Ellis & Young, 2013) and Kircher and Gauggel (2008). When hearing speech, information is acoustically processed, then compared to existing representations in the acoustic input lexicon. Next, representations are activated in the semantic system along the semantic network and made accessible. A matching representation can be selected and then contextually integrated on a higher-order level. Whether top-down regulation of lower-order processes, such as the spreading of semantic network activation, is possible, is debated (Kircher & Gauggel, 2008).

**The neural correlates of speech processing** have been historically examined by lesion studies, identifying a complex frontotemporal network for language processing. Important regions to name are the left inferior frontal gyrus (IFG) with the Broca Area (traditionally associated with motor speech function), the left superior temporal gyrus (STG) with the Wernicke Area (traditionally associated with sensory language function), the middle temporal gyrus (MTG), the gyrus angularis, and their respective right-hemispheric analogues (Kircher & Gauggel, 2008). A left-hemispheric lateralization of language is found in most right-handed people (Hickok & Poeppel, 2007; Hodgson & Hudson, 2018).

However, further studies have shown that language is **differentially processed in the left and right hemispheres**. According to Beeman (Beeman, 1998; Beeman &

Chiarello, 1998), the left hemisphere contains the main semantic lexicon, where target content is activated shortly but strongly for fast accessibility, namely for fine semantic coding of familiar, conventional stimuli. On the other hand, the right hemisphere represents more ambiguous semantic information such as metaphors for coarse semantic coding that is less strongly but more continuously accessible. The **dual-stream model** similarly proposes the functional differentiation of a ventral and a dorsal processing stream after the bilateral auditory (dorsal STG) and phonological (superior temporal sulcus [STS]) processing. The dorsal stream, consisting of the posterior IFG, the premotor cortex, and the Spt (Sylvian parietal temporal) area, converts sensory information into articulatory and motor information. The ventral stream comprises the anterior MTG and the inferior temporal sulcus (ITS) as a combinational network and the posterior MTG and ITS as the lexical interface that transforms sensory information into lexical meaning. The dorsal stream is predominantly left-lateralized, while the ventral stream is bilaterally structured (Hickok & Poeppel, 2007; Hodgson & Hudson, 2018; Rilling et al., 2012).

In conclusion, speech processing relies on intact function and interaction of sensory, semantic, lexical, and higher-order abilities such as context processing and pragmatics[1]. Relevant brain regions are located in the temporal cortex as well as in the inferior frontal gyrus. Left and right hemispheres on the one hand, and ventral and dorsal streams on the other hand, are believed to play differential roles in the processing of speech.

---

[1] In linguistics, pragmatics refers to “the ability to use language and other expressive means to convey meaning in a specific interactional context” (Bosco et al., 2018)

## 2.3. Speech perception in schizophrenia spectrum disorders

Deficits in speech perception and comprehension have been consistently observed in patients with schizophrenia.

One of the main characteristics of SSD is the disruption of thought and language. Abnormalities of speech production such as derailment, incoherence, and illogicality are characterized under the term "**Formal Thought Disorder**" (FTD) and are assessed using positive symptom scores (Andreasen, 1984b). In this chapter, we will give an overview on speech processing impairments in SSD and one of the most prominent features of FTD in SSD, disturbed perception of abstractness.

### 2.3.1. Speech processing in patients with SSD

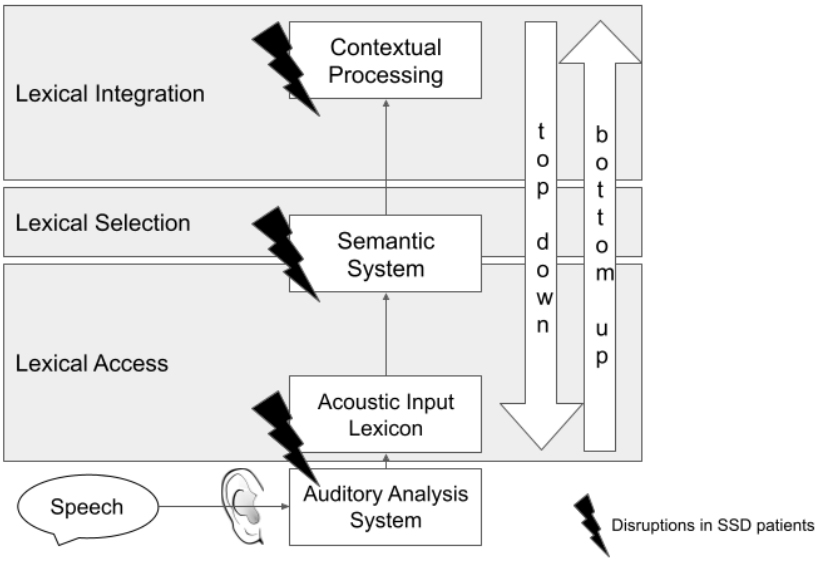


Figure 2: Speech processing in SSD patients

A schematic and simplified illustration of the processes involved in speech perception and comprehension, with elements from Ellis and Young (Ellis & Young, 2013) and Kircher and Gauggel (2008) (see Figure 1). The flashes mark suggested disruptions in SSD patients that cause impaired speech processing (Kircher & Gauggel, 2008).

Abnormalities of speech perception have been detected on different levels of processing (see figure 2): impaired auditory processing, dysfunctional semantic system causing aberrant lexical access and selection, and higher-order dysfunctions impeding contextual processing. For an investigation of these processes, mismatch paradigms are especially useful in that they normally induce well-studied reactions in healthy samples that can be regarded as measures of intact processing.

On an auditory level, **mismatch negativity**, an acoustically evoked electrophysiological potential as a response to an unexpected deviation in a sound pattern, is reduced in SSD patients in comparison to healthy controls. This also applies for speech sounds and is associated with structural abnormalities of the Heschl's gyrus[2] and the planum temporale (Kasai, Shenton, et al., 2003; Kasai, Yamada, et al., 2003; Koshiyama et al., 2020; Yamasue et al., 2004). Possible explanations are sensory memory deficits which make processing of longer stimuli difficult. Besides, disturbed discrimination of acoustic stimuli could cause a sensory overload that impedes speech comprehension. (Kircher and Gauggel, 2008).

Event-related potentials (ERP) can also be used to acquire a neural correlate of speech processing. For this purpose, sentences with a short logical storyline can be presented (“He met his brother in their favorite bar”). If the last word of the sentence is replaced by an unrelated word (“He met his brother in their favorite milk”), healthy subjects react with a negative EEG potential after 400 ms, which is deemed to reflect the spreading activation of the semantic network (Kutas & Federmeier, 2011). Patients with schizophrenia tend to exhibit increased latency and lower amplitude of the **N400 potential** (Kircher & Gauggel, 2008; Kostova et al., 2005; Mathalon et al., 2002; Mohammad & DeLisi, 2013).

Dysfunctions of the semantic network have also been shown in **priming studies**. Schizophrenia patients showed **hyperpriming** for indirectly related words with short intervals, i.e., access to targets that are indirectly related to the prime (e.g., “chair - stand” via “sit”) is facilitated. This might represent a possible correlate of loosened association (Kuperberg et al., 2018; Minzenberg et al., 2002). In fMRI studies, patients showed enhanced signals in temporal and prefrontal areas for primed versus non-primed targets, although healthy controls showed the opposite pattern as a sign of reduced processing effort for primed stimuli (Kuperberg et al., 2007). SSD patients lack the ability to actively inhibit irrelevant meanings in the semantic network, especially of ambiguous words, so that they tend to attribute the most common, but not the contextually correct meaning (Gernsbacher et al., 1999; Salisbury, 2010).

---

[2] Part of the auditory cortex in the temporal lobe (Warrier et al., 2009)

Also, it was suggested that problems of **pragmatics,** the ability to transport contextual meaning beyond the explicit words said (Bosco et al., 2018), and discourse comprehension might contribute to their difficulties in extracting higher-order meaning out of sentences and understanding references (Kircher & Gauggel, 2008; Langdon et al., 2002; Parola et al., 2020).

**Structural abnormalities** in language related cortical areas support the notion that disturbances of speech perception are due to neural dysfunctions: the planum temporale, the STG, parahippocampal and fusiform gyrus show less asymmetric volumes in schizophrenia patients' than in healthy controls' brains, which points to a reduced lateralization of the language network (Kircher & Gauggel, 2008; McDonald et al., 2000; Shenton et al., 2001; Sommer et al., 2001).

These aberrations show that SSD patients not only have difficulties understanding abstract language, but also processing deviant/mismatching auditory or semantic input as a consequence of multi-level neural disturbances.

### 2.3.2. Abstract language

One of the most characteristic language impairments that can be classified as an FTD in SSD patients is their difficulty in comprehending abstract language.

**Abstract language** refers to mental concepts without a tangible form, e.g., 'peace' and 'freedom'. According to Lakoff and Johnson (2008), words used to describe these abstract ideas are at all times based on metaphoric concepts and can, thus, be considered metaphors themselves. This definition allows a careful comparison of different forms of abstract language, including figurative language, metaphors, idioms, and proverbs.

Difficulties in understanding such abstract language have long been observed in schizophreniform disorders (for a review, see: Rossetti et al., 2018). Metaphors, especially, are often wrongfully taken literally. Patients displaying this kind of thought disorder named **"Concretism"** struggle with extracting the higher-level meaning behind figurative language, also including idioms, proverbs, and irony (Bambini et al., 2020; Barth & Küfferle, 2001; Mossaheb et al., 2014; Rapp et al., 2013). For example, the phrase "He is a night owl" can be used to describe a person who prefers staying up late. The listener is required to extract this figurative meaning over the literal meaning of the words, according to the context. Frequent misinterpretation of figurative phrases constitutes a major barrier in day-to-day communication as we habitually rely on these stylistic devices to express ourselves.

A reliable tool to diagnose concretism is the proverb interpretation test developed by Barth and Küfferle (2001). Concretism ratings seem to be directly related to clinical acuity and severity of schizophrenic symptoms (Brackmann et al., 2020; Sela et al., 2015; Siddi et al., 2016). In addition, concretism is correlated with thought disorder and negative symptoms, possibly indicating that the ability to communicate is impaired on multiple levels (Iakimova et al., 2006; Langdon et al., 2002; Mossaheb et al., 2014).

Several fMRI experiments have been undertaken to elucidate the neural processes underlying concretism by contrasting sentences with metaphoric and literal content. Their results suggest an aberrant recruitment of the **left IFG** and the **temporal lobe** for metaphoric stimuli in schizophrenia patients (Kircher et al., 2007; Rossetti et al., 2018; Thoma & Daum, 2006). Mashal et al. (2013) showed that for novel metaphors, patients excessively activated the left IFG in contrast to controls, who rather engaged the right IFG. The activity of the left IFG further correlated with concretism ratings and metaphor comprehension (Kircher et al., 2007; Mashal et al., 2013). Some researchers argue that **lateralization abnormalities** of the language network may play a part in impeding abstract language comprehension in schizophrenia (Chakrabarty et al., 2014; Mitchell & Crow, 2005). For example, magnetoencephalography (MEG) and split visual field studies have revealed that the right hemisphere is overactive in schizophrenia patients during comprehension of novel metaphors, which may imply that coarse semantic processing of unfamiliar, non-conventionalized stimuli is advantaged at the expense of conventional stimulus processing (fine semantic coding) (Zeev-Wolf et al., 2014; Zeev-Wolf et al., 2015).

## 2.4. Neural processing of gestures

A simple self-experiment can make one aware of the great influence of gestures on everyday communication: hide your hands behind your back or under a table for a whole conversation. Conveying a thought or finishing a sentence might become unexpectedly hard. Not only do **gestures help listeners understand** the speaker's message by accentuating keywords and illustrating a communicative intent; these versatile hand movements also **support the speaker's thought process** and hence influence the ability to retrieve information and learn (Goldin-Meadow, 2015, 2017; Goldin-Meadow & Alibali, 2013). Moreover, children express themselves with their hands even before they speak their first words, which is deemed beneficial for **language development** (Iverson & Goldin-Meadow, 2005; Özçalışkan & Dimitrova, 2013; Özçalışkan & Goldin-Meadow, 2005). The tight interconnection even indicates that speech originally derived from gesture (Gentilucci & Corballis, 2006). Successful **social interaction** is strongly shaped by the appropriate use of gestures. Especially in SSD, impaired communication can have wide-ranging effects on patients' social functionality and rehabilitation (Walther et al., 2016; Walther & Mittal, 2016).

**Gestures** are particular visual stimuli that convey semantic meanings within hand motion. They can either inherit an individual meaning independent of speech, as in emblematic or pantomime gestures, or be accompanied by abstract or concrete speech as in metaphoric and iconic co-verbal gestures (McNeill, 1992). **Metaphoric gestures**, as defined by McNeill (1992) accompany abstract language by displaying a form or object that figuratively illustrates the meta-level meaning of the sentence. For instance, interlocking two fingers depicts a close friendship in the statement "The friends are inseparable". However, if the same gesture accompanies a concrete phrase, e.g., "The chains are firmly connected", it is classified as an **iconic gesture**.

The following passage focuses on the **neuroscientific mechanisms** of gesture perception in healthy study samples (Andric & Small, 2012; Yang et al., 2015).

As close as the evolutionary origins of gesture and speech are considered to be, as similar are their neural characteristics (Gentilucci & Corballis, 2006; Gentilucci & Dalla Volta, 2008). Meaningful iconic stimuli, both gestures and spoken speech, are processed in a common system extending from the left IFG to bilateral temporal regions (Straube et al., 2012). Furthermore, gestures incongruent to accompanying speech induce a more negative N400 response in ERP experiments compared to congruent gestures, which also corroborates the similarities between speech and gesture processing (Fabbri-Destro et al., 2015; Holle & Gunter, 2007; Kelly et al., 2004; Özyürek, 2014; Proverbio et al., 2015).

The **integration** of meaningful **iconic gestures** and **corresponding speech** (bimodal stimuli versus unimodal stimuli) elicited BOLD (blood-oxygen level dependent, see chapter 3.3.) activation in the left posterior **MTG** in fMRI (He et al., 2015). It was demonstrated that the connectivity between auditory and visual gesture processing sites (MTG and occipital cortex) is modulated by the STS (Straube et al., 2018). The idea that the **STS** and **STG** play a facilitating role in integrating speech and gesture, especially under challenging hearing conditions, is supported by other studies (Holle et al., 2010; Özyürek, 2014).

Simultaneous EEG and fMRI investigation revealed a two-stepped correlation between BOLD signals and alpha power[3], implying that gesture-speech integration takes place in the posterior STS/MTG region at an earlier stage and is subsequently continued in the left IFG (He et al., 2018).

Converging evidence indicates that **metaphoric gesture perception** elicits activation in the **left IFG** (Andric et al., 2013; Nagels, Chatterjee, et al., 2013; Nagels, Kauschke, et al., 2013; Straube et al., 2011; Straube, He, et al., 2013; Villarreal et al., 2008) and temporal areas (Andric et al., 2013; Nagels, Chatterjee, et al., 2013; Skipper-Kallal et al., 2015; Straube et al., 2011; Straube, He, et al., 2013), whereas iconic gestures mainly involve the bilateral MTG (Nagels, Chatterjee, et al., 2013; Straube et al., 2011).

Some studies suggest overlaps between the iconic and metaphoric gesture conditions in superior temporal and inferior parietal regions (Andric et al., 2013; Straube et al., 2011; Villarreal et al., 2008).

These findings are in line with the **semantic unification theory** proposing the engagement of the posterior temporal lobe for the semantic integration of familiar, over-learned stimuli like iconic gestures, for which a mental representation already exists. The disparate semantic information in metaphoric gestures (abstract language combined with concrete meaningful hand movement), however, requires to be unified to a novel mental representation. This semantic unification process is

---

[3] Amount of oscillations in the alpha frequency range (7-13 Hz) in EEG examination (He et al., 2018)

deemed to take place in the left inferior frontal gyrus (Hagoort et al., 2009; Straube et al., 2011; Willems et al., 2009).

The semantic unification theory was originally implemented to explain results from semantic **speech-gesture mismatch** studies. When contrasting meaningful co-verbal gestures (matches) to semantically unrelated or meaningless co-verbal gestures (mismatches), differential involvement of the posterior STS and MTG on the one hand and the left IFG on the other hand was observed. It was suggested that the STS and MTG are responsible for the **semantic integration** of common, familiar semantic representations (speech, pantomimes, related co-speech gestures), while the left IFG shows higher activation for less related (mismatching) co-speech gestures, which need a new, on-line **semantic unification** of the input streams. The higher the integration load (the further the semantic relation), the higher the activation of the IFG needed for constituting a novel representation (Hagoort et al., 2009; Özyürek, 2014; Willems et al., 2007, 2009).

Mismatch studies analyzed the **N400 response** in ERP to gestures accompanying speech (Özyürek et al., 2007). The N400 signal, which is known as an indicator of semantic mismatch processing, was demonstrated to be less negative in ambiguous sentence contexts when accompanied by a congruent, disambiguating gesture than by an incongruent gesture, showing that gestures can reduce the processing effort for verbal language (Holle & Gunter, 2007; Özyürek, 2014).

In this way, speech-gesture mismatch paradigms can help to elucidate the integration of multimodal communicative input.

| STG/MTG | IFG |
|---|---|
| Semantic integration | Semantic unification |
| Conventional stimuli<br>● integration of information streams into preexisting representation | Unconventional, new stimuli<br>● unification of information streams into newly built representation |
| Examples:<br>● related co-verbal gestures<br>● iconic co-verbal gestures | Examples:<br>● unrelated co-verbal gestures<br>● metaphoric co-verbal gestures |

Figure 3: The semantic unification theory (Hagoort et al., 2009; Willems et al., 2009) according to Straube et al., 2011, modified and simplified.

Multimodal stimuli with low integration load due to familiarity or conventionality can be integrated in the temporal lobe. Stimuli with higher integration load (unrelated or metaphoric gestures) have to be processed onto a new mental representation (semantic unification). STG, superior temporal gyrus (left, upper light gray area); MTG, middle temporal gyrus (left, lower light gray area); IFG, inferior frontal gyrus (right, dark gray area).

## 2.5. Gesture deficits in schizophrenia spectrum disorders

Deficits in gesture production and perception have been consistently reported in SSD patients. Throughout the course of disease, SSD is linked to defective gesturing: Gesture impairment has been observed in adolescents at ultra-high risk for psychosis (Millman et al., 2014). Moreover, severity increased with the number of psychotic episodes and chronicity (Stegmayer, Moor, et al., 2016; Walther et al., 2016).

Both **imitation[4] and pantomime[5] of gestures** are perturbed in schizophrenia (Colle et al., 2013; Dutschke et al., 2017; Martin et al., 1994; Matthews et al., 2013; Park et al., 2008; Walther et al., 2013a, 2013b, 2015; Walther & Mittal, 2016). Walther et al. (2013b), for example, implemented the test of upper limb apraxia (TULIA) to assess schizophrenia patients' ability to correctly perform gestures. They reported that 67% of their patient sample exhibited deficits in imitating and pantomiming according to their cut-off score. Furthermore, natural co-verbal gesturing and nodding are significantly reduced in patients (Lavelle et al., 2013; Troisi et al., 1998).

Multiple behavioral experiments have also confirmed patients' **impaired recognition of gestures** (Berndl et al., 1986; Karakuła et al., 2013; White et al., 2016). SSD patients tend to misinterpret incidental movements as meaningful gestures (Bucci et al., 2008) and to refer observed gestures to themselves, notably if given ambiguous communicative cues (White et al., 2016). Patients with gesture deficits also display reduced social perception and gesture recognition ability, pointing to a generalized disruption of nonverbal communication in schizophrenia (Walther et al., 2015).

Gesture impairment is correlated with certain **symptom categories**. For instance, it has been demonstrated that gesture deficits are related to the severity of **negative symptoms** (e.g., affective flattening, alogia, apathy) (Lavelle et al., 2013; Matthews et al., 2013; Park et al., 2008; Walther et al., 2016). Gesture performance and nonverbal social perception can even serve as outcome predictors, forecasting social functionality and negative symptom progression after six months (Walther et

---

[4] The examined person first observes a gesture performed by another party without additional verbal explanation (e.g., placing the palm of the right hand on to the right ear), and is then asked to reproduce the identical gesture.

[5] The examined person is asked to perform a gesture based on a verbal command (e.g., "Pretend to be using scissors to cut paper").

al., 2016). This interrelation is supported by findings confirming that movement therapy can improve negative symptoms in schizophrenia (Martin et al., 2016).

Gesture perception is also linked to **positive symptoms** (e.g., formal thought disorders, delusion, hallucinations). Patients with severe hallucinations report lower confidence when interpreting a gesture (White et al., 2016), and communicative delusions are associated with the misinterpretation of movement as meaningful gestures (Bucci et al., 2008). Pronounced positive formal thought disorder[6] is related to a reduced ability to distinguish matching and mismatching abstract speech-gesture combinations (Nagels et al., 2019).

Some possible **neural correlates** of gesture impairment have been investigated so far: for instance, some studies relate **working memory deficits** to gestural malfunctioning in schizophrenia (Matthews et al., 2013; Park et al., 2008). Also, **motor abnormalities** seem to be associated with perturbed gesturing (Dutschke et al., 2017; Walther et al., 2015). Gesture imitation, especially, was linked to catatonia as well as to extrapyramidal motor symptoms (Walther et al., 2013a). Moreover, connections between aberrant gesture production and **frontal lobe function** (Walther et al., 2013a, 2013b) have been discussed. The particular correlation between pantomime performance and frontal lobe function was explained by an increased task demand when transferring a verbal command to manual motion (Walther et al., 2013a).

The role of the **IFG** and the **temporal lobe** within the integration of speech and gesture in schizophrenia has been analyzed by comparing bimodal (speech and gesture) to isolated unimodal (speech or gesture) conditions (Straube, Green, et al., 2013; Wroblewski et al., 2019). It was found that the integration of **metaphoric gestures** and corresponding abstract speech is impaired in patients, demonstrated by less activation in the left-hemispheric posterior MTG and IFG in comparison to controls (Straube, Green, et al., 2013). Also, **neural connectivity** from the left superior temporal sulcus (STS) to the bilateral IFG is disrupted for the perception of metaphoric, but intact for iconic gestures (Straube, Green, et al., 2014). More recent findings, however, suggest that the gesture-speech integration network previously confirmed in a healthy sample, involving the posterior STS, visual occipital cortex,

---

[6] Positive formal thought disorder refers to disorganized thinking, as opposed to negative formal thought disorder, which subsumes symptoms of impoverished thinking (J. Chen et al., 2021)

and auditory cortex (MTG), is functional in SSD patients. Only the connection between left MTG and STS, referred to as the “verbal pathway”, is impeded in SSD and even correlated with concretism ratings and negative symptom rating scores (Wroblewski et al., 2019).

Both the IFG and the MTG are part of the left-hemispheric **“praxis network[7]”** associated with gesture planning (Bohlhalter et al., 2009). A recent study showed a significant correlation between gesture performance and functional connectivity between the bilateral STG in healthy study participants. In comparison, no correlation with gesture performance, but a decreased connectivity of these regions was confirmed in schizophrenia patients (Wüthrich, Viher, et al., 2020). Furthermore, gesture deficits were predictable by disturbances of white matter tract connectivity in the praxis network. Especially the connectivity between the bilateral IFG was reduced in the schizophrenia group (Viher et al., 2020). These findings support the notion that gesture impairment could be attributed to **functional abnormalities** in the frontotemporal network.

These results are in line with imaging studies showing that gesture impairment, in general, is associated with **anatomical abnormalities** (gray matter loss and cortical thinning) e.g. in the IFG, anterior cingulate cortex (ACC), STG and MTG (Stegmayer, Bohlhalter, et al., 2016; Viher et al., 2018).

---

7 A “left lateralized fronto-temporo-parietal network” activated by gesture processing and production in healthy subjects (Wüthrich, Viher, et al., 2020)

## 2.6. Speech-gesture mismatch detection

A growing body of evidence has demonstrated that the investigation of **gesture-speech mismatches** contributes to the understanding of speech and gesture integration (Green et al., 2009; Holle et al., 2008; Özyürek, 2014; Straube, Meyer, et al., 2014; Willems et al., 2007). On the one hand, the comparison of matching (related) versus mismatching (unrelated) speech and gesture allows for the identification of neural areas relevant for **integrating meaningful semantic information**. On the other hand, mismatches compared to matches are suspected to elicit the activation of additional brain areas responsible for **new or semantically unrelated stimuli**.

The perception of mismatched gesture and speech has been associated with activity of the **left IFG** in healthy samples (Green et al., 2009; Hagoort et al., 2009; Hein et al., 2007; Holle et al., 2008; Özyürek, 2014; Willems et al., 2007, 2009). As mentioned earlier, it has been hypothesized that the IFG is responsible for the increased processing demand of new, unfamiliar semantic stimuli that require the unification of two, disparate information streams, as is the case in mismatches (Willems et al., 2009). First mismatch studies using audiovisual stimuli in schizophrenia patients revealed increased signals in frontal and insular areas (Surguladze et al., 2001) and aberrant engagement of the right-hemispheric motor-speech area including the IFG and STG for mismatches (Szycik et al., 2009). This might reflect a compensatory hyperactivation for the increased processing effort in SSD patients.

Dysfunctions of the IFG, as found in SSD with regards to abstract speech and metaphoric gestures, could also contribute to impaired mismatch detection performance.

The ability to understand the semantic relationship between verbal and non-verbal information such as speech and gestures is relevant for successful social communication. It is based on the successful integration and comprehension of multimodal semantic inputs and is therefore a promising subject to research. It can be investigated using **relatedness assessment** (Schülke & Straube, 2017) or **mismatch detection tasks** (Nagels et al., 2019; Steines et al., 2021). In both tasks, the relatedness between gesture and speech semantics has to be evaluated, either on a Likert-like scale from 1 (low relatedness) to 7 (high relatedness) (Schülke & Straube, 2017) or in a categorical manner (‘related’/‘unrelated’) in mismatch detection tasks (Nagels et al., 2019). These tasks have the advantage that both information sources have to be taken into account to successfully perform the task. The paradigm also allows for the manipulation of speech-gesture relatedness and semantic abstractness.

In a previous study, Nagels et al. (2019) used the mismatch detection paradigm to investigate the **gesture-speech mismatch detection performance** in SSD. It has been demonstrated that patients make more errors than controls when judging the relatedness of gesture and accompanying speech. This finding was also confirmed in a transcranial direct current stimulation (tDCS) study applying a relatedness assessment task (Schülke & Straube, 2019). In this task, patients demonstrated a reduced rating accuracy in relatedness evaluations compared to healthy control subjects. Regarding abstract content, only symptom specific effects could be found in the large sample of Nagels et al. (2019): Patients exhibiting severe formal thought disorder performed worst in abstract conditions of the gesture-speech mismatch detection task.

**Intervention studies** have already observed an increase of patients’ rating accuracy in the relatedness assessment task by inhibitory tDCS of the left frontal lobe (Schülke & Straube, 2019). However, to date, the brain regions involved in impaired mismatch detection are still unidentified.

Overall, it can be assumed that SSD patients have a considerable deficit in **interpreting abstract speech and metaphoric gestures** as well as in **integrating multimodal communicative input**. This leads to impeded social interaction and symptom progression. The neural defect accompanying this phenomenon might be malfunctioning of the **IFG** and **temporal areas** of the language network. However, the neural correlates of gesture-speech matching processes of concrete and abstract utterances accompanied by related or unrelated gestures are still unknown.

## 2.7. Aims of the study

The investigation of the neural processes underlying speech-gesture mismatch detection in abstract and concrete sentence contexts in SSD might shed new light on the pathology of gesture impairment, which is associated with a range of symptoms typical to psychosis and is likely to contribute to poor social interaction in SSD.

In the long run, this investigation might pave the way towards therapies that incorporate speech and gesture therapies (Riedl et al., 2020) as well as neural stimulation methods to ameliorate communicative abilities and symptom progression.

The **aim of this study** is to clarify the distinct disturbances that are related to patients' difficulties in understanding and interpreting abstract and concrete speech-gesture combinations. Our innovative study paradigm combines a speech-gesture mismatch detection task with functional imaging and thus offers the advantage of a task- and performance-related examination of neural processes.

The three leading questions we aim to answer are:

A. Can we confirm a reduced ability of SSD patients to judge the relatedness of speech and gesture? Does abstractness influence the results?
B. What are the neural correlates of SSD patients' difficulties discriminating between related and unrelated speech-gesture combinations?
C. Do SSD patients have dysfunctional processing of abstract/metaphoric speech-gesture combinations?

According to the leading questions, the hypothesis, results, and discussion sections will each be organized into three main parts.

**Part A** will focus on the behavioral results: whether SSD patients have reduced task performance, and how response behavior varies between groups and semantic contexts (abstract/concrete).

In **part B**, we aim to explore the neural dysfunctions that underlie impaired mismatch detection performance. For this, we will focus on the processing of unrelated in contrast to related speech-gesture combinations. What similarities do both groups have in the neural processing of mismatches? Which regions exhibit lower or higher engagement in the SSD group compared to the control group?

In **part C**, we are interested in the differential processing of abstract in contrast to concrete speech-gesture pairs, as they are expected to carry an increased processing demand that SSD patients might not be able to fully meet (Straube, Green, et al., 2013). What do SSD patients have in common with healthy controls, which may reflect a starting point for successful therapeutic interventions? Where do SSD patients show lower, and where higher activation than healthy subjects?

## 2.8. Hypotheses

The following hypotheses were formulated with regard to the aforementioned questions:

**A.** Based on previous findings (Nagels et al., 2019), we hypothesized that SSD patients would show reduced task performance in the mismatch detection task in both abstract and in concrete sentence contexts.

**B.**

  a. On a neural level, we hypothesized that in both groups, perception of unrelated speech and gesture (mismatches) would result in higher frontal activation than the perception of semantically related pairs, due to an increased processing demand (Green et al., 2009; Willems et al., 2009).

  b. Yet, we expected the processing of mismatches to elicit either less activation in the frontal cortex in patients compared to healthy controls, reflecting impaired multimodal integration, or

  c. higher activation for an increased processing effort (Surguladze et al., 2001; Szycik et al., 2009).

**C.**

  a. We expected that both groups would engage some common activation of the frontotemporal network for abstract versus concrete stimuli as a sign of partly functioning processing. As recent studies showed partially intact connectivity of the temporal lobe in SSD patients (Straube, Green, et al., 2014; Wroblewski et al., 2019), we anticipated these activations in the STG and MTG.

  b. However, we hypothesized that SSD patients, compared to controls, would show reduced activation in the IFG in response to abstract stimuli, causing disturbed abstractness processing and multimodal integration (Straube, Green, et al., 2013, 2014).

  c. We also hypothesized that SSD patients would not show higher frontal activation than controls for abstract versus concrete stimuli.

# 3. Methods

## 3.1. Study sample

### 3.1.1. Patients

A total of 42 patients (9 female, mean age = 34.3, SD = 11.1, range = 19-57, see Table 1) diagnosed with schizophrenia (n = 30), schizoaffective disorder (n = 11) and other non-organic psychotic disorder (n = 1) according to ICD-10 (F20, F25, F28) or DSM-IV (295.X) criteria, recruited from 2012 to 2019, were included in our final analysis.

Initially, a study sample of n = 57 patients was recruited and assessed by psychiatrists and psychologists of the Department of Psychiatry and Psychotherapy, Philipps-University Marburg. Fifteen patients were excluded from our final analysis (exclusion criteria: missing responses [≥ 10%] in behavioral task [n = 2], signal dropouts in functional images [n = 3], excessive movement during fMRI data acquisition [defined as > 1.5 mm relative movement or > 3 mm absolute movement, n = 10] (Power et al., 2014, 2015; Soares et al., 2016; Wilke, 2014)).

All 42 patients were German native speakers (three bilinguals), four were left-handed, 24 were high school graduates. In the Multiple-Choice Word Test B (MWT-B) (Lehrl et al., 1995), patients achieved a mean score of 27.7 (SD = 7.5). Symptoms were assessed according to the Scales for Assessment of Positive Symptoms (SAPS, n = 39, mean sum = 19.74, SD = 19.1) and Negative Symptoms (SANS, n = 41, mean sum = 23.05, SD = 21.2) (Andreasen, 1984b, 1984a). All patients were clinically stable under antipsychotic medication (mean dose in chlorpromazine equivalents = 735.65 mg/day, SD = 1355.17) (Leucht et al., 2016). Patients with a self-reported or documented history of psychiatric disorders were included if SSD was their main diagnosis.

All subjects were free of visual and auditory deficits and did not suffer from any additional neurological impairment. Cerebral integrity was assessed by a T1-weighted MRI sequence; the T1 was missing for four patients due to technical issues.

### 3.1.2. Healthy Control Group

Thirty-six out of 50 healthy control subjects (11 female, mean age = 36.8, SD = 11.2, range = 20-56) were included in the final analysis. Fourteen subjects were excluded (exclusion criteria: missing responses [≥ 10%] in behavioral task [n = 1], incidental abnormalities in T1-weighted MRI [n = 1], signal dropouts in functional images [n = 6], excessive movement during the fMRI paradigm [n = 6]).

All subjects were German native speakers (two bilinguals), one was left-handed and 23 were high school graduates. Patients and controls were matched for education (see Tab. 2). They achieved a mean score of 30.9 (SD = 3.4) in the MWT-B, which was not significantly different from the patient sample (see appendix: Supplementary table 1 for participants' neuropsychological test performance). Participants did not have any visual or auditory deficits, neurological or psychiatric disorders. T1-images of six subjects were missing due to technical issues.

This study was approved by the local Ethics Committee (file numbers 55/10 and 05/15) and written informed consent was obtained from all participants (patients and healthy control subjects). They were paid an allowance of 50 euro for participation.

Table 2: Sociodemographic characteristics

N, number of participants; f, female; m, male; SD, standard deviation of the mean; SAPS, Scale for Assessment of Positive Symptoms; SANS, Scale for Assessment of Negative Symptoms; CPZ, chlorpromazine; MAO-inhibitor, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

| Variable | | Patient group | Control group |
|---|---|---|---|
| N | | 42 | 36 |
| Sex f/m | | 9/33 | 11/25 |
| Age (SD) | | 34.4 (11.1) | 36.8 (11.2) |
| Years of Education (SD) | | 11.8 (1.5) | 12.1 (1.5) |
| Highschool graduates | | 24 | 23 |
| Left-handed | | 4 | 1 |
| Smokers | | 25 | 8 |
| SAPS sum (SD) n = 39 | | 19.7 (19.1) | |
| SANS sum (SD) n = 41 | | 23.1 (21.2) | |
| Antipsychotic medication in CPZ equivalents (SD) | | 735.65 (1355.17) | |
| Antipsychotic medication | | | |
| Number of patients receiving | Atypical antipsychotics | 37 | |
| | Typical antipsychotics | 0 | |
| | Other antipsychotics | 2 | |
| Psychiatric medication (other than antipsychotics) | | | |
| Number of patients receiving | MAO-Inhibitor | 1 | |
| | Tricyclic antidepressants | 1 | |
| | SSRI | 6 | |
| | SNRI | 2 | |
| | Bupropion | 2 | |
| | Agomelatine | 1 | |
| Duration of illness in years (SD) n = 25 | | 9.68 (8.79) | |
| Number of hospitalisations n = 18 | | 1.94 (1.51) | |

## 3.2. Stimuli

The stimuli consisted of 160 video clips, each depicting the same actor speaking a German sentence and simultaneously performing a manual gesture. The material has been described and successfully used in several behavioral (Nagels et al., 2019), tDCS (Schülke & Straube, 2017, 2019) and fMRI studies (Green et al., 2009; Kircher et al., 2009; Straube et al., 2009, 2011; Straube, Green, et al., 2013). Part of it has been used in fMRI studies using implicit tasks (Green et al., 2009; Kircher et al., 2009; Straube et al., 2008, 2011; Straube, Green, et al., 2013). Each of the clips had a duration of 5 seconds and contained 0.5 seconds without speech or movement both before and after the sentence was presented. Phrase and co-verbal gesture were demonstrated in a naturalistic way with the actor facing the camera. German sentences were grammatically structured in the style of ‘subject - predicate - object’.

As in previous behavioral (Nagels et al., 2019) and tDCS studies (Schülke & Straube, 2017, 2019), four different types of speech-gesture combinations were chosen for this experiment. The speech content could either be abstract, as in “the conversation is on a high level”, or concrete, such as in “the building is high”. While for the latter example, the adjective ‘high’ represents an actual measurable altitude, the same adjective embedded into an abstract context illustrates the difficulty of a sophisticated conversation. Hence, each video was classified as abstract (metaphoric gesture) or concrete (iconic gesture) (McNeill, 1992). Furthermore, the relationship between speech and co-verbal gesture was categorized as related when the statement was accompanied by a semantically matching gesture, or as unrelated when the gesture did not match the co-occurring speech. Consequently, the four conditions were characterized as follows (see Figure 4):

(1) Abstract speech and related metaphoric gesture (AR, abs/rel)
(2) Abstract speech and unrelated gesture (AU, abs/unr)
(3) Concrete speech and related iconic gesture (CR, con/rel)
(4) Concrete speech and unrelated gesture (CU, con/unr)

To countervail possible sequence effects, two stimulus sets of 80 videos each were generated. For every set, 20 videos of each condition (20 x 4) were presented in a pseudo-randomized and counterbalanced order. Each sentence appeared only once per set, either with a related or unrelated gesture. Each subject saw only one set.

In a preliminary rating study, all videos were assessed by a group of 20 healthy, German native speakers concerning their abstractness, relatedness, and familiarity. For a detailed description of the implemented stimuli, see Nagels et al. (2019).

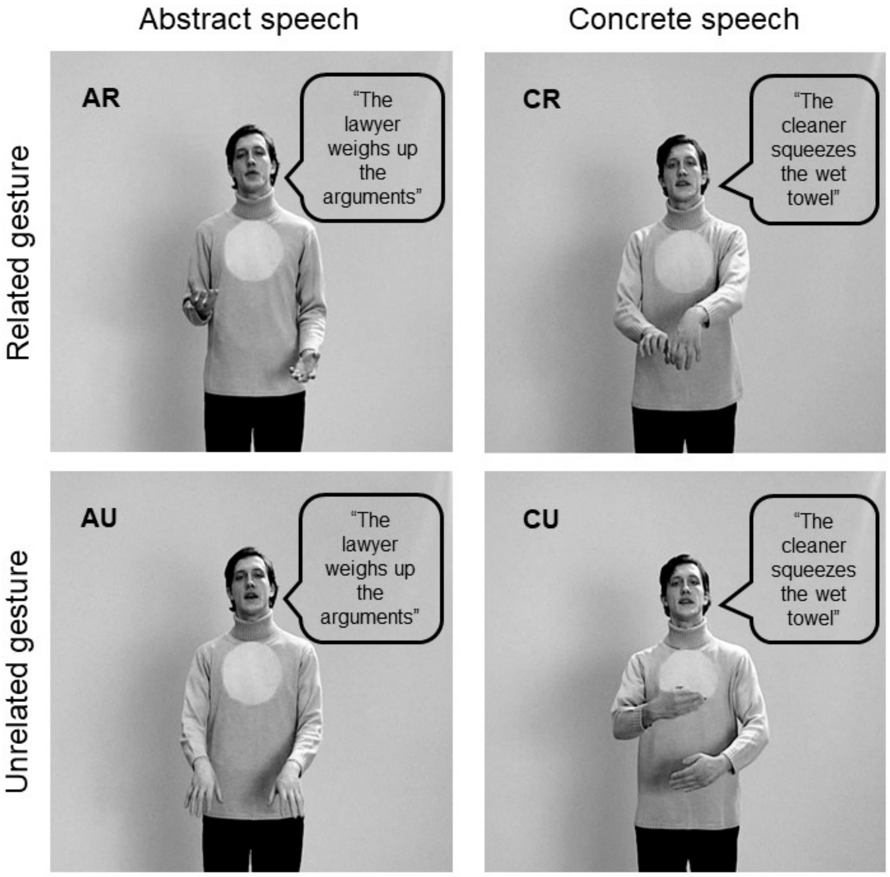


Figure 4: Video conditions

Four types of gesture-speech combinations.

**(1)** abstract related, AR

**(2)** abstract unrelated, AU

**(3)** concrete related, CR

**(4)** concrete unrelated, CU

## 3.3. Functional magnetic resonance imaging

Before explaining the details of the experimental design, a general overview on functional magnetic resonance imaging will be given in this paragraph.

Functional MRI unites the advantage of being non-invasive without exposure to radiation, with a good temporal and excellent spatial resolution in comparison to non-invasive alternatives like electroencephalography (Kircher & Gauggel, 2008). Potential, but well preventable hazards are magnet-related accidents and implant dislocation, as well as heating of metal and tissue. Contraindications for fMRI acquisition include ferromagnetic material in body parts, e.g. pace makers, metallic implants, and claustrophobia. With all precautions taken, MRI is considered a very safe procedure (Sammet, 2016).

Magnetic resonance imaging makes use of the effect of magnetic fields and radiofrequency on hydrogen protons in organic tissue. Electrons flowing in a coil induce a magnetic field. Hydrogen protons are positively charged and act as magnets when placed into that magnetic field. The spin orientations of the protons, which were originally random, will then align either in the same direction or in the opposite direction of the magnetic field (longitudinal direction). A very slight majority of protons will be oriented parallel to the magnetic field, resulting in a net magnetization in the longitudinal direction (Pooley, 2005).

In MRI, radiofrequency pulses (energy pulses resulting from rapidly changing magnetic and electric fields) cause the spins of the protons to orient away from the longitudinal direction towards the transverse direction. The net magnetization decreases in the longitudinal direction and increases in the transverse direction, resulting in a rotation of the magnetization, referred to as the flip angle (Pooley, 2005; Prabhakar, 2016). After the radiofrequency pulse is applied, the protons will gradually reorient towards the longitudinal direction of the magnetic field (longitudinal relaxation). The time constant T1 describes the rate at which the longitudinal magnetization is reached. T2 is the time constant that determines the rate at which excited protons go out of phase after the radiofrequency pulse has caused in-phase precessions. The MR-signal is emitted in the form of electric currents induced by magnetization. As T1 and T2 are characteristics individual to the kind of tissue, they can be used for imaging in gray scales (Pooley, 2005; Preston, 2016).

MR-images can be obtained by applying radiofrequency pulses in certain sequences and slice by slice of the examined object. The repetition time (TR) determines the amount of time between the pulses applied to one slice. The echo time (TE) describes the time between the pulse and the following signal in the coil (Preston, 2016). The matrix size is defined by the number of rows (phase direction, y-gradient) and columns (frequency direction, x-gradient) in the Field of View (FoV), the size of the covered area. The slice thickness defines the depth of the resulting three-dimensional cubes (voxels) (Rinck, 2022; Yeung & Murphy, 2011).

In this study, MRI data were acquired using echo planar imaging (EPI) sequences, which are obtained by switching of gradient polarity instead of radiofrequency pulses and allow for rapid imaging with high temporal resolution and reduced motion artifacts, making them suitable for functional MR imaging (Bashir & Feger, 2012).

Functional imaging is a temporally delayed representation of local blood oxygen levels that are thought to be indirectly associated with brain function, making use of the blood-oxygen level dependency (BOLD) effect (Logothetis et al., 2001; Ogawa et al., 1990; Pauling, 1935).

The magnetic susceptibility of organic material depends on the physical properties characteristic to the kind of tissue. Material with strong magnetic susceptibility is termed ferromagnetic, whereas material with weak magnetic susceptibility is paramagnetic. While deoxygenated blood is paramagnetic due to the exposed iron ion, oxygenated blood is diamagnetic (i.e., has no magnetic susceptibility) (Runge, 2018).

Localized neural activity first leads to a decreased oxygen level in that area, which then triggers an increase of localized cerebral blood flow and an augmented oxygen level about 5 seconds delayed to the actual activity. This causes a decrease in magnetic susceptibility and a subtle increase in the MR signal. This pattern is visualized in the hemodynamic response function (HRF) which depicts the BOLD-changes in the course of time (Kircher & Gauggel, 2008; Runge, 2018).

For practical application, study participants are presented with a study paradigm stimulating certain areas of the brain; e.g., in our study, videos of a person performing gestures. The participants are also asked to give responses to a specific question after each video. This will cause an increase and decrease of hemoglobin oxygenation in localized brain areas according to the hemodynamic response function. The task paradigm can be synchronized to data acquisition, enabling an investigation of brain activation during the task.

In the case of this study, we acquired BOLD data during the presentation of abstract and iconic related and unrelated gestures and finger-tapping a response, so involvement of the visual and auditory cortices as well as the motor cortex can be expected. However, we are more specifically interested in how language-related areas differentially engage during the various conditions. For this purpose, the HRFs following each speech-gesture video presentation were individually measured. Every video, and hence every HRF was categorized to one of four video types (AR, AU, CR, CU). When interested in a single condition compared to a baseline, the contrast between the averaged signal obtained from one condition (e.g., AR) and the signal obtained from a control condition (e.g., a gray field) can be calculated. Further, the difference between experimental conditions can be analyzed by contrasting, e.g., all unrelated stimuli (AU, CU) to all related stimuli (AR, CR). By doing so, general cortex activation will be canceled out and subtle differences between the conditions can be unveiled (Kircher & Gauggel, 2008; Runge, 2018).

## 3.4. Experimental design

For the fMRI experiment, we provided participants with earplugs and headphones to reduce scanner noise. Videos were displayed on an MRI-compatible screen using Presentation® software (Version 18.3, Neurobehavioral Systems, Inc.), made visible via a mirror attached to the head coil.

To best detect changes in BOLD-response across the experimental conditions, an event-related design was chosen. During fMRI data acquisition, subjects observed 20 stimuli of each of the four conditions in a pseudo-randomized order. Every 5 s video was followed by a blank gray screen (low-level baseline) for 5000 ms on average (variable between 3750 - 6750 ms) resulting in a total duration of 14 min for the experiment.

For each video, subjects were asked to determine whether the presented gesture and spoken sentence were semantically matching or not. Responses were given via button press on an MR-compatible answering device attached to the left thigh. Participants were instructed to respond only after the video had disappeared from the screen. Mismatch ratings were indicated by the left index finger, and match ratings by the left middle finger.

Before the experiment, every subject underwent four practice trials outside the scanner to ensure the correct understanding and implementation of the instructions. None of these videos were included in the subsequent testing material.

## 3.5. fMRI data acquisition

MRI data were collected using a Siemens 3 Tesla MR Magnetom Trio Trim scanner. Functional data were obtained applying a T2-weighted echo-planar imaging (EPI) sequence (repetition time [TR] = 2000 ms; echo time [TE] = 30 ms; flip angle = 90 deg). The volume included 33 transversal slices (slice thickness = 3.6 mm; interslice gap = 0.36 mm; field of view [FoV] = 230 mm, voxel resolution = 3.6 $mm^2$). 420 volumes were acquired for each subject. Subsequently, T1-weighted anatomical images were obtained. Ten participants' T1 images are missing for technical reasons.

## 3.6. Data analysis

### 3.6.1. Behavioral data analysis (Part A)

First, behavioral data from all subjects were checked for completeness. Since each subject was presented with and had to rate a total of 80 stimuli, subjects with more than seven missing responses (≥ 10% of all responses) were excluded from further analysis (n = 3). Following signal detection theory (Stanislaw & Todorov, 1999), the detection rate *d'* was then calculated to determine the sensitivity of each subject for differentiating between related and unrelated stimuli in abstract and concrete contexts:

$d' = z(hitrate) - z(falsealarmrate)$. For this calculation, hits were defined as the number of correctly identified related items (AR and CR, respectively) and false alarms as the number of unrelated items (AU and CU) incorrectly identified as related. This resulted in individual detection rates (*d')* for both the abstract and the concrete conditions. A higher *d'* value indicates a better discrimination of related and unrelated stimuli, while a *d'* of zero would indicate no discrimination between the two.

In addition, the response criterion *c* was calculated to account for individual response bias in both the abstract and the concrete conditions: $c = -1/2 * [z(hitrate) + z(falsealarmrate)]$. A positive *c* value would indicate a participant being more critical and less likely to perceive speech and gesture as related. In contrast, a negative *c* value would signal a higher tendency to rate speech and gesture as related.

A repeated-measures ANOVA of *d'(abs)* and *d'(con)* values was performed in a 2 x 2 design with abstractness (abstract/concrete) as within-subject factor and group as between-subject factor (patients/controls) to test the hypothesis that patients demonstrate a reduced ability to differentiate between related and unrelated speech-gesture combinations (Hypothesis A). The same statistic was performed for *c(abs)* and *c(con)*, hit rates [*H(abs)* and *H(con)*] and false alarm rates [*F(abs)* and *F(con)*], for a better exploration of the participants' response behavior.

### 3.6.2. fMRI data analysis (Parts B and C)

To ensure the quality of the recorded data, all structural and functional files were visually inspected for artifacts, neuropathology, or any other abnormalities. At this stage, one subject out of the original study sample was excluded due to an incidental finding and nine more due to signal dropouts.

Functional MRI data were, then, analyzed using the Statistical Parametric Mapping software (SPM12, v6685, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/, RRID: SCR_007037) implemented in MATLAB 7.9.0 (release 2009b, The MathWorks, Inc., RRID: SCR_001622). To avoid saturation effects, the first five images of the measurement were discarded from the analysis.

First, all functional data were realigned to the mean image of the run. Next, images (with the mean image as reference) were normalized to the Montreal Neurological Institute (MNI) space (defined by tissue probability maps), resulting in a resliced voxel size of 2 $mm^3$. Lastly, smoothing was performed with an 8 $mm^3$ Gaussian kernel to adjust for anatomical variance between subjects. After preprocessing, realignment parameters were checked for excessive movement (defined as volumes with > 1,5 mm relative movement or > 3 mm absolute movement) (Power et al., 2014, 2015; Soares et al., 2016; Wilke, 2014). Consequently, 16 subjects out of the original sample were excluded from further analysis.

On a single-subject level, the onset of each event was defined as the integration point, i.e., the time when the stroke of the gesture coincides with the corresponding keyword of the spoken sentence (Green et al., 2009). All 80 events were modeled with a duration of 1 second and assigned to one of the four conditions (AR, AU, CR, CU). For a similar approach, see Nagels et al. (2015). Movement parameters were included as multiple regressors to correct for artifacts due to head movement during data acquisition. The time between two videos was not modeled, thus serving as an implicit low-level baseline. This approach has been successfully implemented in previous experiments (Green et al., 2009; Nagels, Chatterjee, et al., 2013; Straube et al., 2008).

#### 3.6.2.1 Group analysis

Contrast images (baseline contrasts) for the four conditions were entered into a flexible-factorial analysis, considering group (patients, controls) as a between-subject factor and conditions (abstractness x relatedness: AR, AU, CR, CU) as within-subject factors 2 x 2 x 2 design). Age was included as a covariate of no interest (see appendix chapter 8.2.2 for design matrix).

A Monte-Carlo-Simulation (acquisition matrix: x = 64, y = 64; slices: 33; DIM: xy = 3.58 mm, z = 3.96 mm; FWHM = 13.4 mm; DIM resampled = 2 mm, no mask, iterations: 1000) was performed to calculate the minimum voxel contiguity threshold needed to correct for multiple comparisons at $p < 0.05$, assuming an individual voxel type I error of $p < 0.05$ (Slotnick, 2017; Slotnick et al., 2003). Consequently, a cluster extent threshold of 1308 contiguous resampled voxels at $p < 0.05$ (whole-brain analysis) was used for all contrasts of interest (see appendix chapter 8.2.3).

Voxel coordinates reported are located in MNI space and for anatomical location, functional data were referenced to the Automated Anatomical Labeling toolbox in SPM12 (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002). For further statistical analyses of neural and behavioral data, SPSS (version 24.0) for Linux was utilized.

### 3.6.2.2 Contrasts of interest

#### 3.6.2.2.1. Part B

For the contrast of unrelated > related conditions, a conjunction was calculated to examine group similarities (Hypothesis B.a.) and interaction *T*-tests were performed to clarify group differences (Hypothesis B.b. and B.c.).

*(1) C(unr > rel) ∩ P(unr > rel)*

Using a conjunction analysis, we tested the hypothesis that the perception of unrelated speech and gesture would elicit higher frontal activation than the perception of semantically related pairs in both groups, due to an increased processing demand (Green et al., 2009; Willems et al., 2009) (Hypothesis B.a.).

*(2) C(unr > rel) > P(unr > rel)*

Using an interaction analysis (T-test), we tested the hypothesis that controls would show higher frontal activation for mismatches versus matches than controls. reflecting impaired multimodal integration (Hypothesis B.b.)

*(3) P(unr > rel) > C(unr > rel)*

The interaction analysis (T-test) was performed to test whether patients would show higher frontal activation than controls for mismatches versus matches as a sign of an increased processing effort (Surguladze et al., 2001; Szycik et al., 2009) (Hypothesis B.c.).

#### 3.6.2.2.2. Part C

For the contrast of abstract > concrete conditions, conjunctions were calculated to examine group similarities (Hypothesis C.a.), and interaction T-tests were performed to clarify group differences (Hypothesis C.b. and C.c.).

*(4) C(abs > con) ∩ P(abs > con)*

Using conjunction analysis, we tested the hypothesis that both groups would demonstrate common frontotemporal activation for abstract versus concrete stimuli (Straube, Green, et al., 2014; Wroblewski et al., 2019) (Hypothesis C.a.).

*(5) C(abs > con) > P(abs > con)*

The interaction analysis was performed to test whether SSD patients, compared to controls, would show reduced activation in the left IFG in response to abstract stimuli, indicating impaired abstractness processing and multimodal integration (Straube, Green, et al., 2013, 2014) (Hypothesis C.b.).

*(6) P(abs > con) > C(abs > con)*

The interaction analysis tested the hypothesis that patients do not show higher frontal activation than controls for abstract versus concrete stimuli (Hypothesis C.c.).

# 4. Results

## 4.1. Part A (Behavioral data)

### 4.1.1. Detection rates

Overall, patients exhibited significantly lower detection rates *d’* compared to healthy controls (rm-ANOVA, between-subjects effect: $F(1, 76) = 16.31$, $p < 0.001$; post-hoc-tests, *d’abs*: $t(76) = 3.975$, $p < 0.001$; *d’con*: $t(76) = 3.292$, $p = 0.002$; two-way, see Table 3 and Figure 5). However, there was no significant main effect of abstractness, indicating comparable performance across abstract and concrete conditions (rm-ANOVA: $F(1, 76) = 1.95$, $p = 0.167$). The interaction of group and abstractness, likewise, did not reach significance ($F(1, 76) = 0.02$, $p = 0.882$).

### 4.1.2. Hit rates and False alarm rates

Patients exhibited lower hit rates and higher false-alarm rates than control subjects. Specifically, the repeated measures ANOVA of hit rates determined a significant group difference ($F(1,76) = 4.113$, $p = 0.046$), but no main effect of abstractness ($F(1,76) = 2.179$, $p = 0.144$). In the post-hoc T-test, there was only a significant group difference for the abstract hit rates ($t(66.992) = 2.729$, $p = 0.008$). For the false-alarm rates, the main effects of abstractness ($F(1,76) = 9.326$, $p = 0.003$) and group ($F(1,76) = 0.306$, $p = 0.008$) were significant. Post-hoc *T*-tests revealed significant differences in both sentence contexts (abstract: $t(76) = -2.107$, $p = 0.038$; concrete: $t(76) = -2.875$, $p = 0.005$, see Figure 5). These results support the notion that SSD patients have difficulties in judging the relatedness of gesture and speech in general. This is represented by a reduced ability to correctly identify matching speech-gesture combinations and an increased inclination to falsely rate mismatches as matches.

### 4.1.3. Response criterion

The response criterion for abstract and concrete conditions was negative for both groups, indicating a general tendency to rate gesture and speech as related to each other more often than not (see Table 3). In addition, the repeated measures ANOVA revealed a significant main effect of abstractness, with the response criterion being more negative for the abstract conditions (*F*(1, 76) = 10.017, *p* = 0.002, Greenhouse-Geisser-correction). This means that both, patients and controls, were more inclined to judge abstract speech-gesture combinations as related, while they were more critical when judging concrete combinations.

No significant interaction of abstractness and group (*F*(1, 76) = 1.816, *p* = 0.182, Greenhouse-Geisser-correction) and no significant main effect of group were found (*F*(1,76) = 0.364, *p* = 0.548).

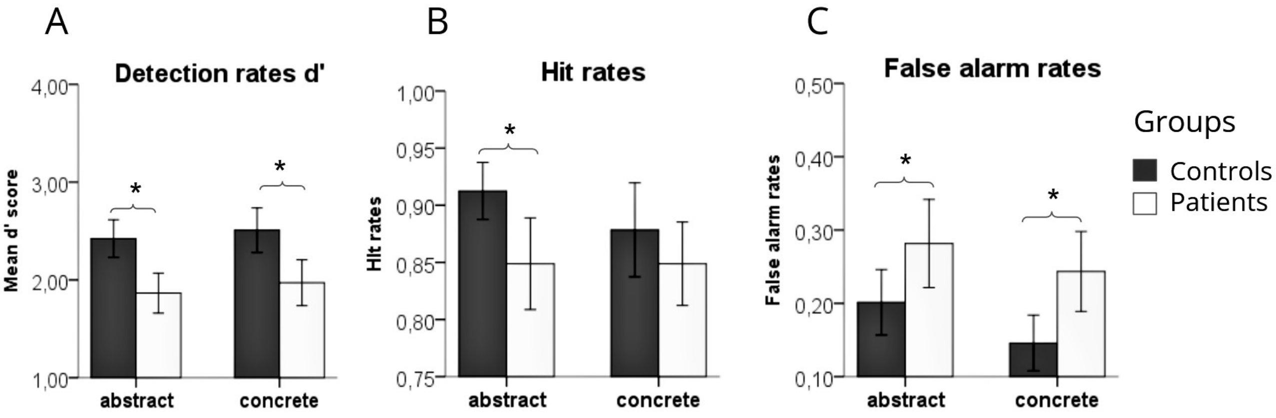


Figure 5: Detection rates, hit rates and false alarm rates

A: Detection rates d’, B: Hit rates (rate of correctly identified related items), and C: False alarm rates (rates of incorrectly identified unrelated items) for abstract and concrete conditions. Black bars: control group. White bars: patient group. Error Bars: 95% CI of the mean. *Significance level p < 0.05 (uncorrected) in post-hoc T-tests.

Table 3: Detection rates d’ and response criterion c.

Repeated measures ANOVA was performed with abstractness as within-subject factor and group as between-subject factor. *p-values of post-hoc two-way T-tests (uncorrected).

*Detection rates (d') and response criterion (c)*

| | | Patients | Controls | *p*-value* |
|---|---|---|---|---|
| d' | abstract (SD) | 1.87 (0.66) | 2.42 (0.57) | <0.001 |
| | concrete (SD) | 1.97 (0.75) | 2.51 (0.68) | 0.002 |
| c | abstract (SD) | -0.26 (0.51) | -0.27 (0.38) | 0.231 |
| | concrete (SD) | -0.18 (0.44) | -0.06 (0.40) | 0.946 |

## 4.2. Part B: fMRI data (relatedness)

### Effects of relatedness (unrelated > related)

(4) Controls and patients: *C(unr > rel) ∩ P(unr > rel)*

The conjunction analysis revealed common activation in the two groups for unrelated > related stimuli in bilateral medial segments of the superior frontal gyri (MSFG) and rostral supplementary motor area (SMA) (Figure 6, I, Table 4).

(5) Controls > patients: *C(unr > rel) > P(unr > rel)*

The interaction analysis showed that controls exhibited increased activation in the right SMA, the bilateral ACC and left precentral gyrus for unrelated > related stimuli compared to patients (Figure 6, II, Table 4).

(6) Patients > controls: *P(unr > rel) > C(unr > rel)*

The reverse interaction revealed activations in right hippocampal, superior temporal regions, and left superior, middle and inferior frontal, bilateral cerebellar and parietal regions in patients > controls (Figure 6, III, Table 4).

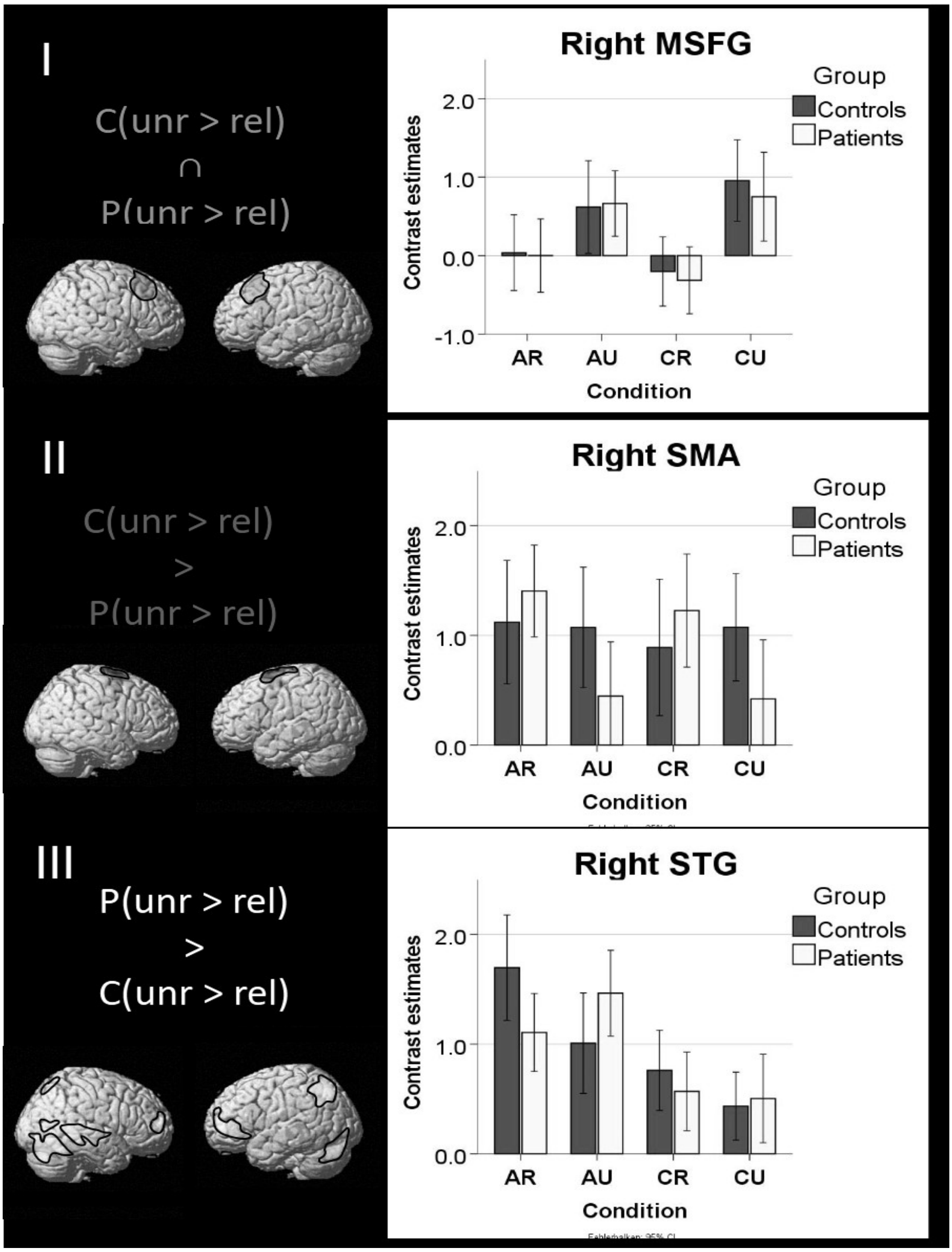


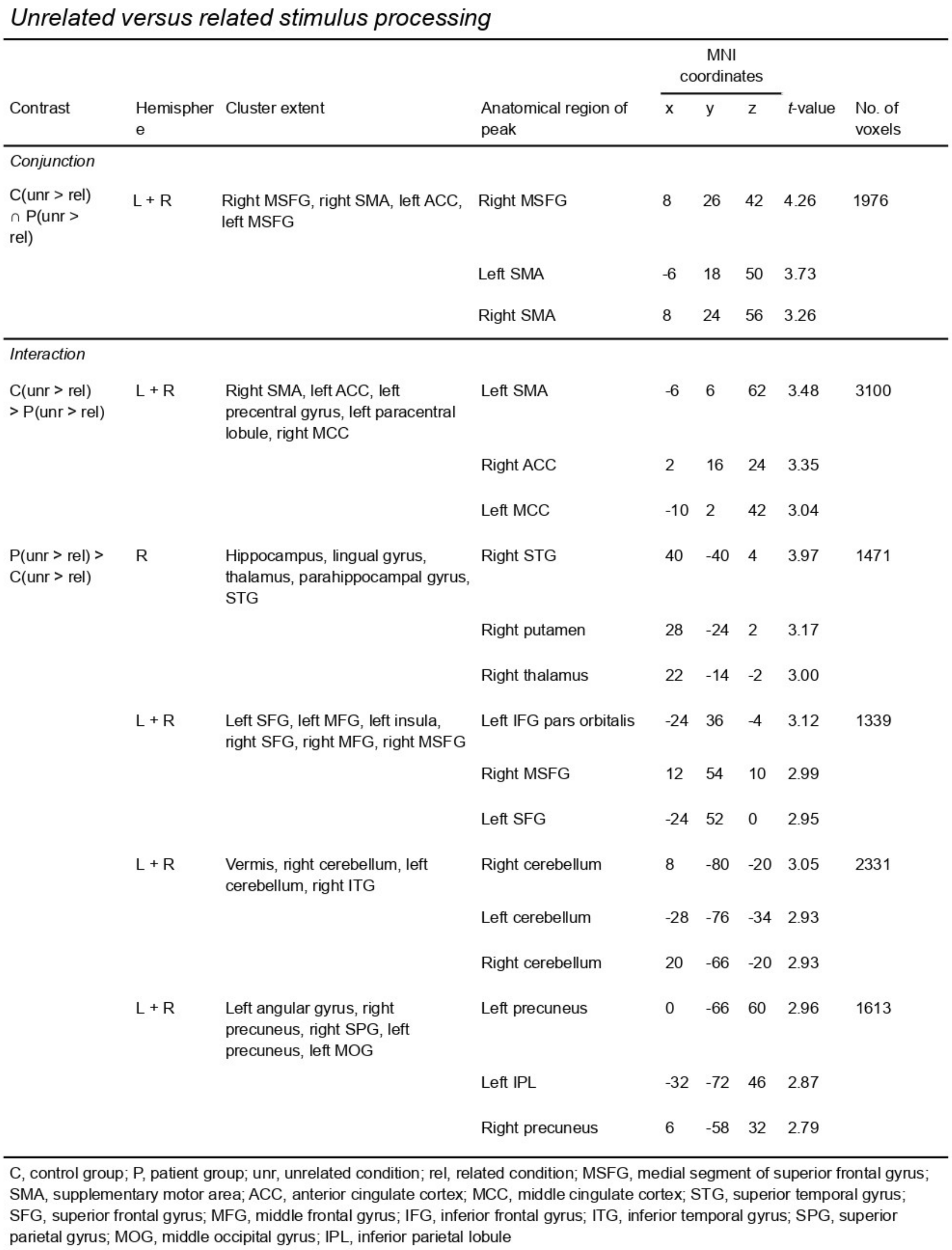
Figure 6: Activation patterns for unrelated > related stimuli

Left: Activation patterns for the contrast unr > rel (unrelated stimuli [AU and CU] > related stimuli [AR and CR]) in controls and patients (I), controls > patients (II), and patients > controls (III). Right: Contrast estimates of the peak activated regions of each contrast, based on the extracted eigenvariate of activated clusters in respectively masked analyses (masks from WFU PickAtlas) using the VOI function in SPM12. Dark gray bars: control group. Light gray bars: patient group.

AR = abstract related, AU = abstract unrelated, CR = concrete related, CU = concrete unrelated. Error bars: 95% CI of the mean.

Table 4: fMRI results for unrelated versus related stimulus processing

fMRI clusters resulting from the between-group conjunction and between-group interactions of unrelated > related speech-gesture pairs, corrected at $p < 0.05$. For each cluster, MNI coordinates and t-values of the first peak voxel are listed. Anatomical regions refer to peak voxel localization based on the AAL toolbox (local maxima labeling) and cluster extent to the cluster labeling.



*Unrelated versus related stimulus processing*

| | | | | MNI coordinates | | | | |
|---|---|---|---|---|---|---|---|---|
| Contrast | Hemisphere | Cluster extent | Anatomical region of peak | x | y | z | *t*-value | No. of voxels |
| *Conjunction* | | | | | | | | |
| C(unr > rel) ∩ P(unr > rel) | L + R | Right MSFG, right SMA, left ACC, left MSFG | Right MSFG | 8 | 26 | 42 | 4.26 | 1976 |
| | | | Left SMA | -6 | 18 | 50 | 3.73 | |
| | | | Right SMA | 8 | 24 | 56 | 3.26 | |
| *Interaction* | | | | | | | | |
| C(unr > rel) > P(unr > rel) | L + R | Right SMA, left ACC, left precentral gyrus, left paracentral lobule, right MCC | Left SMA | -6 | 6 | 62 | 3.48 | 3100 |
| | | | Right ACC | 2 | 16 | 24 | 3.35 | |
| | | | Left MCC | -10 | 2 | 42 | 3.04 | |
| P(unr > rel) > C(unr > rel) | R | Hippocampus, lingual gyrus, thalamus, parahippocampal gyrus, STG | Right STG | 40 | -40 | 4 | 3.97 | 1471 |
| | | | Right putamen | 28 | -24 | 2 | 3.17 | |
| | | | Right thalamus | 22 | -14 | -2 | 3.00 | |
| | L + R | Left SFG, left MFG, left insula, right SFG, right MFG, right MSFG | Left IFG pars orbitalis | -24 | 36 | -4 | 3.12 | 1339 |
| | | | Right MSFG | 12 | 54 | 10 | 2.99 | |
| | | | Left SFG | -24 | 52 | 0 | 2.95 | |
| | L + R | Vermis, right cerebellum, left cerebellum, right ITG | Right cerebellum | 8 | -80 | -20 | 3.05 | 2331 |
| | | | Left cerebellum | -28 | -76 | -34 | 2.93 | |
| | | | Right cerebellum | 20 | -66 | -20 | 2.93 | |
| | L + R | Left angular gyrus, right precuneus, right SPG, left precuneus, left MOG | Left precuneus | 0 | -66 | 60 | 2.96 | 1613 |
| | | | Left IPL | -32 | -72 | 46 | 2.87 | |
| | | | Right precuneus | 6 | -58 | 32 | 2.79 | |

C, control group; P, patient group; unr, unrelated condition; rel, related condition; MSFG, medial segment of superior frontal gyrus; SMA, supplementary motor area; ACC, anterior cingulate cortex; MCC, middle cingulate cortex; STG, superior temporal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; SPG, superior parietal gyrus; MOG, middle occipital gyrus; IPL, inferior parietal lobule

## 4.3. Part C: fMRI data (abstractness)

### Effects of abstractness (abstract > concrete)

(1) Controls and patients: *C(abs > con) ∩ P(abs > con)*

The conjunction analysis showed that both groups exhibit common activation of left middle temporal areas, right STG, left and right superior frontal gyrus (SFG), bilateral cunei, and posterior cingulate cortices for abstract > concrete stimuli (Figure. 7, I, Table 5).

(2) Controls > Patients: *C(abs > con) > P(abs > con)*

The interaction analysis revealed higher activation in bilateral frontal areas including the precentral gyri and the IFG in healthy subjects compared to patients for abstract compared to concrete stimuli (Figure 7, II, Table 5).

(3) Patients > Controls: *P(abs > con) > C(abs > con)*

The reverse interaction showed patients additionally engaging cerebellar structures for abstract conditions but no increased frontal activation (Figure 7, III, Table 5).

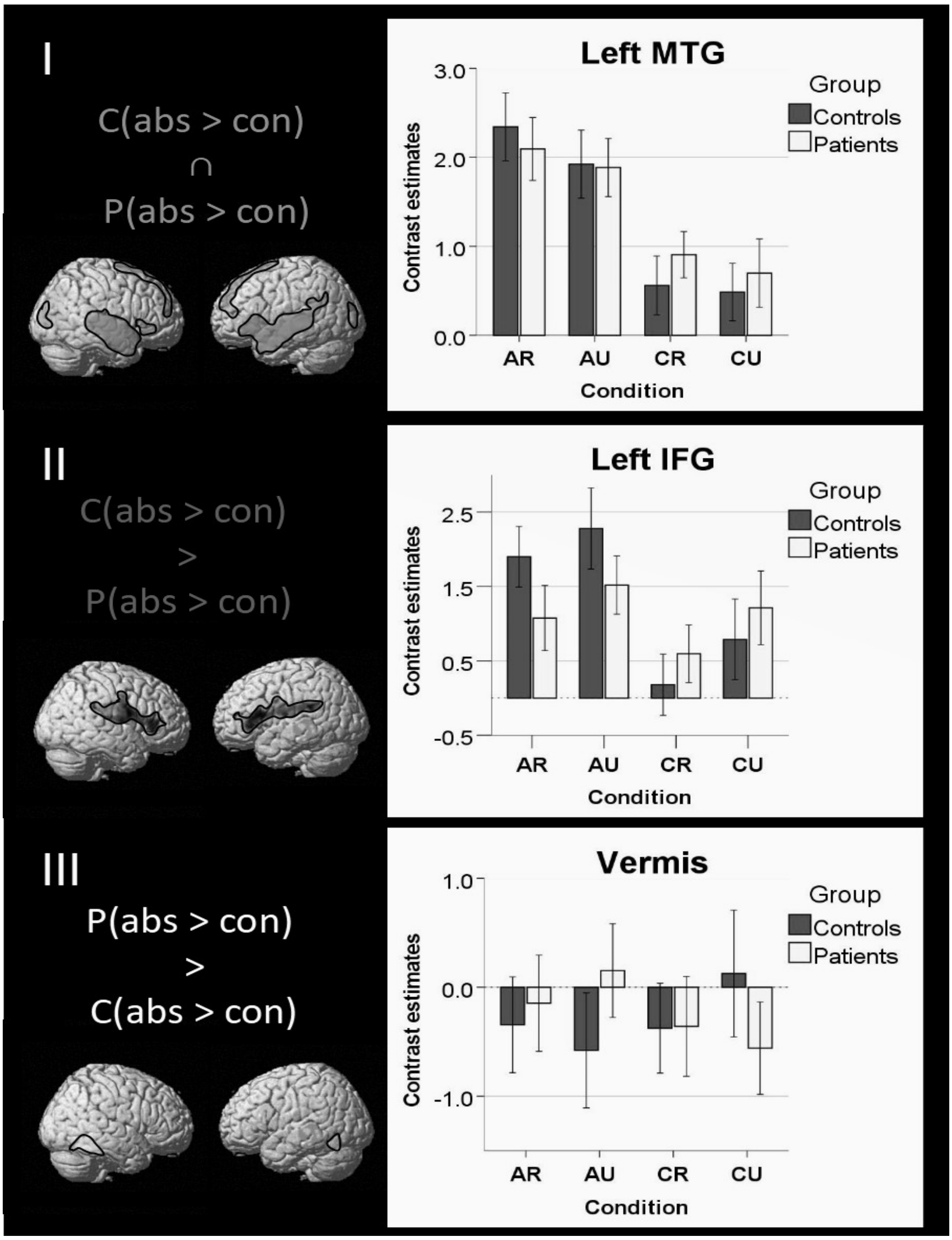


Figure 7: Activation patterns for abstract > concrete stimuli

Left: Activation patterns for the contrast abs > con (abstract stimuli [AR and AU] > concrete stimuli [CR and CU]) in controls and patients (I); controls > patients (II); patients > controls (III). Right: Contrast estimates of the significantly activated regions of each contrast, based on the extracted eigenvariate of activated clusters in respectively masked analyses (masks from WFU PickAtlas) using the VOI function in SPM12. Dark gray bars: control group. Light gray bars: patient group.

AR = abstract related, AU = abstract unrelated, CR = concrete related, CU = concrete unrelated. Error bars: 95% CI of the mean.

Table 5: fMRI results for abstract > concrete stimulus processing

fMRI clusters resulting from the within-group conjunction and between-group interactions of abstract > concrete speech-gesture pairs, corrected at $p < 0.05$ (whole-brain analysis). For each cluster, MNI coordinates and t-values of the first three peak voxels are listed. Anatomical regions refer to peak voxel localization based on the AAL toolbox (local maxima labeling) and cluster extent to the cluster labeling.

*Abstract > concrete stimulus processing*

| | | | | MNI coordinates | | | | |
|---|---|---|---|---|---|---|---|---|
| Contrast | Hemisphere | Cluster extent | Anatomical region of peak | x | y | z | *t*-value | No. of voxels |
| *Conjunction* | | | | | | | | |
| C(abs > con) ∩ P(abs > con) | L | TMP, TSP, IFG p. opercularis, ROL, IFG p. orbitalis, MTG | Left MTG | -50 | -36 | -2 | 7.55 | 5981 |
| | | | Left MTG | -56 | -10 | -12 | 7.15 | |
| | | | Left MTG | -54 | 4 | -16 | 6.41 | |
| | R | TSP, TMP, IFG p. opercularis, MTG, STG, hippocampus | Right STG | 52 | -6 | -12 | 6.35 | 4596 |
| | | | Right STG | 60 | -10 | 0 | 5.55 | |
| | | | Right TSP | 50 | 12 | -22 | 5.25 | |
| | L + R | Right MSFG, right SMA, right SFG, left MSFG | Left SFG | -12 | 56 | 28 | 4.62 | 1986 |
| | | | Left SMA | -6 | 10 | 70 | 4.22 | |
| | | | Left SFG | -12 | 32 | 56 | 3.13 | |
| | L + R | Left cuneus, right cuneus, vermis, left lingual gyrus, right precuneus, right calcarine sulcus, left SOG, left MCC, right PCC | Left PCC | -4 | -44 | 28 | 4.18 | 6378 |
| | | | Right calcarine | 14 | -78 | 12 | 3.49 | |
| | | | Left precuneus | -6 | -72 | 34 | 3.3 | |
| *Interaction* | | | | | | | | |
| C(abs > con) > P(abs > con) | L | PrG, IFG pars orbitalis, postcentral gyrus, insula, IFG pars triangularis | Left insula | -36 | -8 | 18 | 3.99 | 2918 |
| | | | Left IFG p. triangularis | -52 | 20 | 14 | 3.10 | |
| | | | Left IFG p. triangularis | -36 | 26 | 12 | 3.00 | |
| | R | PrG, insula, IFG pars orbitalis, Heschl gyrus, MFG | Right PrG | 48 | 0 | 20 | 3.74 | 3733 |
| | | | Right IFG p. triangularis | 44 | 28 | 6 | 3.55 | |
| | | | Right ROL | 42 | -6 | 24 | 3.39 | |
| P(abs > con) > C(abs > con) | L + R | Cerebellum, vermis, fusiform gyrus, parahippocampal gyrus | Vermis | 4 | -54 | -16 | 3.10 | 1844 |
| | | | Right cerebellum | 20 | -46 | -18 | 2.98 | |
| | | | Right cerebellum | 24 | -38 | -24 | 2.74 | |

C, control group; P, patient group; abs, abstract conditions; con, concrete conditions; L, left; R, right; TMP, temporal pole of middle temporal gyrus; TSP, temporal pole of superior temporal gyrus; IFG, inferior frontal gyrus; ROL, rolandic operculum; MTG, middle temporal gyrus; STG, superior temporal gyrus; MSFG, medial segment of superior frontal gyrus; SMA, supplementary motor area; SFG, superior frontal gyrus; SOG, superior occipital gyrus; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; PrG, precentral gyrus; MFG, middle frontal gyrus.

# 5. Discussion

In this fMRI study, we examined the neural processes underlying speech-gesture mismatch detection for abstract and concrete semantic contexts in SSD patients and healthy controls. We observed that patients had difficulties in correctly assessing the relatedness between speech and gesture compared to healthy subjects. Interaction analyses revealed a bilateral IFG dysfunction for abstract speech-gesture conditions in patients with SSD. However, both patients and controls showed increased temporal cortex activation for the processing of abstract in contrast to concrete stimuli, suggesting that this area involved in abstractness processing is intact in SSD. While superior frontal cortex activation during mismatch perception was found in both groups, patients still exhibited reduced activity of the SMA and ACC as well as frontotemporal hyperactivation. These neural aberrations may contribute to the observed impaired mismatch detection performance in SSD.

## 5.1. Part A: Behavioral data

### 5.1.1. Detection rates, hit rates and false alarm rates

As expected, overall **lower detection rates** of patients revealed that they had a harder time discriminating between related and unrelated speech-gesture combinations than healthy controls (Hypothesis A). No significant difference between abstract and concrete semantic contexts was found in either group. These results are in line with earlier findings from Nagels et al. (2019), who found the same data pattern for patients with no or only mild formal thought disorders. This supports the conclusion that SSD patients have a **general impairment of speech-gesture relatedness detection** regardless of the semantic context.

Similar results have also been reported in studies investigating the ability to recognize mismatches in spoken sentences (Schneider et al. 2014, Arcuri 2011). Even participants not diagnosed with SSD but scoring high in schizotypy[8]

---

[8] Historically used term to describe schizophrenia-like personality traits and symptoms(Kwapil & Barrantes-Vidal, 2015)

demonstrated longer response times in a semantic relatedness task (de Leede-Smith 2020).

Impairments on different levels of speech and gesture processing can be contributing to this result. According to Ellis and Young (Ellis & Young, 2013), speech processing starts with successful **sensory input**. However, SSD patients exhibit electrophysiological and functional abnormalities in auditory (Jardri et al., 2011; Koshiyama et al., 2020) and visual processing, especially with faces and social situations (Lu et al., 2021; Patel et al., 2020; Yamamoto et al., 2018). Some authors suggest that a sensory overload due to a **sensory gating deficit** prevents patients from focussing on relevant information (Bailey et al., 2021; Kircher & Gauggel, 2008; Vlcek et al., 2014). Needless to say, the integration of the two modalities (speech and gesture) constitutes another barrier in the processing of our stimuli (see chapter 5.3.1).

A large body of evidence confirms **electrophysiological aberrations** for the perception of semantic mismatches during priming experiments, namely altered N400 characteristics (Kostova et al., 2005; Kuperberg et al., 2018; Salisbury, 2010; Schneider et al., 2015; Sharpe et al., 2020). Strikingly, mismatches of gesture and speech evoke the N400 response as well, as studies in healthy subject samples have shown (Fabbri-Destro et al., 2015; Holle & Gunter, 2007; Kelly et al., 2004; Özyürek, 2014; Proverbio et al., 2015). As the N400 signal is deemed to reflect the **semantic network**, it can be hypothesized that SSD patients have a different way of accessing the mental lexicon. Some studies suggest a hyperpriming in the early phases of processing, i.e., unprimed targets elicit abnormally negative potentials, pointing to an overly broad and fast spreading activation within the semantic network (Mathalon et al., 2002; Mohammad & DeLisi, 2013). This could explain how SSD patients have difficulties differentiating between closely related and less related items. Other than that, **memory capacity** plays a considerable role and could thus contribute to disturbed access (Salisbury, 2010). Working memory deficits have been previously reported in SSD (Erickson et al., 2021; Spitzer et al., 1994; Subramaniam et al., 2014); however, the connection with speech-gesture mismatch is yet to be examined.

Moreover, communication requires the higher-order ability to comprehend the **contextual and pragmatic** framework in which speech and gesture are used. Especially gestures, as they are not clearly predefined and have to be understood online, rely on context. Even if the speech and gesture information has been correctly processed individually, implicit knowledge about context and situation complete the overall meaning of the combined items. Impairments of pragmatics and Theory of Mind[9] have often been made accountable for reduced communicative abilities in SSD (Langdon et al., 2002; Parola et al., 2018, 2020) and may also play a part in judging the relatedness of speech and gestures.

SSD patients in our sample showed significantly **lower hit rates as well as higher false alarm rates** when compared to healthy subjects. This allows for the interpretation that patients do not only fail to detect mismatches, but also misinterpret matches of gesture and speech.

On the one hand, patients being impaired when rating related speech-gesture combinations might reflect a **reduced understanding** of their meaning. For abstract sentence contexts, a number of possible causes for dysfunctional semantic processing of figurative language has been proposed. In addition to semantic (Sela et al., 2015) and working memory deficits (Spitzer et al., 1994), impairments of Theory of Mind, executive functions (Bosco et al., 2019; Gavilán Ibáñez & García-Albea Ristol, 2013; Parola et al., 2018; Schettino et al., 2010), and general cognitive functioning (Varga et al., 2014) have been discussed. All these processes could, thus, explain the observed hardships patients showed in recognizing gesture-speech combinations, possibly even in concrete contexts.

On the other hand, patients having difficulties when judging unrelated gestures could be due to a **proneness to misattribution**, as described by Bucci et al. (2008). They reported that patients' tendency to interpret random movement as meaningful was related to delusional experiences. Although we did not examine correlations between task performance and positive symptoms, this should be considered as a possible contributing factor.

Also, more global dysfunctions could contribute to reduced task performance. This theory is supported by evidence showing that patients' underperformance in certain linguistic tasks can be attributed to factors such as **salience of stimuli** (Giora, 2002; Rossetti et al., 2018) or **difficulty of the task** (Iakimova et al., 2005; Ketteler et al., 2012; Yang et al., 2009). This, however, is not fully consistent with the fact that we

---

[9] Theory of Mind refers to "the ability to attribute mental states (ie, beliefs and goals) to one's self and others and to recognize that behaviors are guided by these mental states" (N. C. Andreasen et al., 2008)

did not find a significant difference between abstract and concrete conditions, as abstract stimuli can be considered more difficult to be rated.

### 5.1.2. Response criterion

The analysis of the response criterion showed that both patients and controls have a tendency to rate all gesture-speech combinations as related more often than not. This might be due to a general inclination to give a positive (‘related’) rather than a negative response (‘unrelated’), similar to what is called an ‘**acquiescence bias**’ in socio-psychological surveys (Hinz et al., 2007; Ray, 1983). However, this effect was significantly more pronounced for the abstract conditions, possibly reflecting **increased tolerance when rating abstract** speech-gesture combinations. Metaphoric co-verbal gestures are more likely to be novel and are generally less conventionalized than iconic co-verbal gestures, since they require the transfer of the abstract semantic information to a concrete gesture representation. Therefore, an observer might be more open to new gesture-speech combinations in abstract contexts and, thus, perceive them as related more easily. A concrete sentence, on the other hand, is more likely to elicit the prediction of a specific gesture. This could be violated more easily by a slight variation in movement and lead a subject to judge the gesture as unrelated.

## 5.2. Part B: Relatedness

In our fMRI analysis, the SMA and the ACC showed higher activation for unrelated gesture-speech combinations than for related ones in healthy subjects compared to SSD patients (Hypothesis B.b.). However, the common activation of the rostral SMA and SFG in both groups shows that mismatch processing in this area is partially intact in SSD patients (Hypothesis B.a.). Nevertheless, we also found frontotemporal hyperactivation for this contrast in SSD patients (Hypothesis B.c.).

This is an interesting and novel finding, as these areas both have been associated with gesture perception before, but not yet specifically in patients with SSD in the context of speech-gesture mismatches. A large body of evidence, however, corroborates the important roles of the SMA and ACC in speech and gesture perception, as well as first indications of pathological dysfunctions in SSD.

### 5.2.1. The SMA and motor cortex contributions to speech and gesture processing

While classically assigned to the **motor system**, the SMA's role in speech and language was highlighted more recently by many authors (for a review, see Hertrich et al., 2016). The SMA is involved in **speech control**, lexical selection, as well as linguistic response selection (Alario et al., 2006; Hertrich et al., 2016; Tremblay & Gracco, 2009). Interestingly, the **perception of gestures** was also associated with pre-SMA (anterior part of the SMA) activation (Villarreal et al., 2008). Hertrich and colleagues (2016) reviewed that the pre-SMA especially plays a role in higher-order cognitive functioning.

Anatomically, the SMA is connected to the frontal cortex, namely the SFG and the IFG, by a white matter tract called the **frontal aslant tract** (La Corte et al., 2021). This structural relationship may enable its function in the **language network** (Dick, Bernal, et al., 2014). The SMA, including the pre-SMA, connects cortical language and motor areas (e.g., IFG, premotor, primary motor cortex) with subcortical areas such as the basal ganglia (Dick, Bernal, et al., 2014; Hertrich et al., 2016), making it an important actor in **regulating movement** (Chen et al., 2010; Nachev et al., 2008; Walther et al., 2017).

In SSD, **increased SMA gray matter volume** was found in patients with strong motor deficits (Stegmayer et al., 2014). The corticobasal white matter pathway, which includes the SMA and the ACC, was also abnormal and associated with reduced volitional movement (Bracht et al., 2013). Furthermore, **resting-state hyperperfusion** of the SMA was associated with present catatonia (Walther et al., 2017). The authors suggest that SMA activation might compensate for a disturbed motor circuit. Motor dysfunctions are a common phenomenon in SSD patients with gesture impairment (Donati et al., 2021; Dutschke et al., 2017; Walther et al., 2015), indicating a possible mechanistic overlap.

However, the mentioned experiments focused on gesture/movement production and not on perception or recognition. This being said, the theory that action and perception of gesture engage similar cortical regions ("mirror neuron theory[10]") (Lotze et al., 2006; Rizzolatti, 2005) encourages the theory that speech-gesture perception also relies on motor cortices. In fact, there is evidence for dysfunctions of the mirror neuron network in schizophrenia, in the form of **reduced motor cortex engagement** in action observation (Bagewadi et al., 2018; Enticott et al., 2008; Mehta et al., 2014).

Some authors support the theory that **activation of motor cortices facilitates the comprehension of language** and are especially relevant for action-related words and semantic decision tasks (Du et al., 2016; Vukovic et al., 2017). Therefore, it can be speculated that the reduced activation of the SMA in our study impeded the recognition of speech-gesture mismatches.

Although our data unveiled first promising hints on the relation between speech-gesture recognition and the SMA in SSD, the details have yet to be investigated. Thus, our findings call for a deeper analysis of motor cortex aberrations in gesture-deficient SSD patients.

### 5.2.2. The ACC - dysfunctional conflict processing?

The ACC is diversely involved in **cognitive control functions**, such as performance monitoring, conflict monitoring and decision making (Botvinick et al., 2004; Shenhav et al., 2013). It is hypothesized that the ACC identifies errors or conflicts when increased top-down control is needed (Yeung, 2013). In line with our results, ACC

---

[10] Primate studies have shown that during action observation, the same group of neurons is active as during execution of the same action (Kurata & Tanji, 1986; Rizzolatti et al., 1996). In humans, a group of neurons with similar properties is located in the premotor cortex as well as in the Broca area. Some authors suggest that when observing gestures, a neural representation of the movement is activated in the observer's brain (Buccino et al., 2001, 2004; Rizzolatti, 2005).

activity has been previously invoked by the perception of unrelated iconic gestures in healthy subjects (Straube, Meyer, et al., 2014), reflecting a **surprise reaction** to an unexpected (conflicting) speech-gesture combination. Decreased ACC response could result from patients' reduced ability to differentiate the relatedness of co-verbal gestures. On the one hand, patients might be less surprised by a mismatching speech-gesture combination, since they tend to evaluate them as related and don't recognize the "error". On the other hand, **disturbed error-processing in the ACC** could lead to reduced performance. In fact, there is evidence for impaired error-processing in schizophrenia associated with ACC dysfunctions, which also supports our data (Becerril et al., 2011; Kerns et al., 2005). Intriguingly, semantic incongruence of phrases elicited reduced IFG and ACC response in patients with formal thought disorder compared to those without, possibly reflecting deficits in working memory and conflict monitoring in this patient subgroup (Arcuri et al., 2012; Barch et al., 2000; D'Esposito et al., 2000). This makes the ACC an interesting research subject for cognitive and linguistic tasks in SSD, as its dysfunctions could explain symptoms related to communicative impairment.

### 5.2.3. Frontotemporal hyperactivation

The inadequate engagement of superior temporal and frontal cortices in SSD patients for mismatches might reflect an **increased effort to disambiguate stimuli**, as previously observed in frontal areas during an audio-visual mismatch trial (Surguladze et al., 2001). Here, the semantic unification theory (Hagoort et al., 2009) can be applied to explain how conventionalized stimuli (matches) engage the temporal lobes for semantic integration, while novel stimuli (mismatches) rather depend on the IFG for semantic unification of information streams onto a novel representation. Similarly, mismatch trials with audiovisual stimuli showed right-hemispheric motor speech area aberrations (Szycik et al., 2009) and stronger signals in frontal and insular areas in patients than in controls, speaking for an increased effort to disambiguate visual stimuli (Surguladze et al., 2001). It is possible that this (relative) overactivation is connected to the reduced mismatch detection capacity in patients. In fact, an intervention experiment showed that speech-gesture **rating accuracy could be improved by inhibitory tDCS** of the left frontal lobe (Schülke & Straube, 2019). It can be hypothesized that aberrant activation of the frontal lobe is associated with patients' difficulties in assessing the relatedness of speech and gesture.

Based on our findings, we suspect that tDCS had a modulating effect on the left frontal lobe that increased patients' relatedness judgment capacity, since the IFG is frequently mentioned as a site involved in gesture-speech mismatch processing (Green et al., 2009; Hagoort et al., 2009; Hein et al., 2007; Holle et al., 2008; Özyürek, 2014; Steines et al., 2021; Willems et al., 2007, 2009). The authors suggested either an improvement of the **connectivity between IFG and STS** (Schülke & Straube, 2019; Straube, Green, et al., 2014) or a **downregulation of left frontal hyperactivation**, which our results on mismatch perception (unrelated > related) rather support. How inhibitory stimulation precisely modifies IFG activity, however, still needs further investigation.

## 5.3. Part C: Abstractness

For the contrast of **abstract over concrete stimuli**, a bilateral region including the precentral gyri, IFG, and insulae was less activated in the patient group compared to the control group. It appears that, especially in the left IFG, controls exhibited higher neural engagement during abstract than during concrete stimuli, this effect being less pronounced in patients. As expected, this points to an **abstractness-related IFG dysfunction** in patients (Hypotheses C.b. and C.c.). With these results, we can confirm that the IFG plays an important role in the processing of abstract speech-gesture pairs. However, this specialized function seems to be disrupted in SSD patients.

Our findings align with previous investigations showing involvement of the IFG in the perception of abstract speech and metaphoric gestures.

The impaired perception of **abstract speech** known as concretism has been associated with abnormal function of the IFG in past examinations (Kircher et al., 2007; Rossetti et al., 2018; Thoma & Daum, 2006). Interestingly, Kircher and colleagues (Kircher et al., 2007) reported that schizophrenia patients exhibit activation in a different part of the IFG for metaphors than healthy subjects do. The activity of the left IFG correlated with concretism ratings and metaphor comprehension (Kircher et al., 2007; Mashal et al., 2013). Other authors concluded that higher activation of frontal cortex areas, such as the MFG, might reflect a neural compensatory mechanism for impaired processing of novel metaphors (Mashal et al., 2013). A more recent study, however, indicates that schizophrenia patients show **reduced activation in the left IFG**, but also in bilateral fronto-temporal and parietal cortices, possibly related to altered neural connectivity (Adamczyk et al., 2021), which is consistent with our results. We therefore assume that the IFG dysfunction represents patients' difficulties to process abstract semantic information.

Also consistent with our findings, **metaphoric gestures** in healthy study participants evoked activation in the left IFG in previous investigations (Andric et al., 2013; Kircher et al., 2009; Nagels, Chatterjee, et al., 2013; Nagels, Kauschke, et al., 2013; Straube et al., 2011; Straube, He, et al., 2013; Villarreal et al., 2008), whereas the IFG in SSD patients was found to be less activated for the integration of metaphoric gestures with accompanying speech when compared to healthy controls (Straube, Green, et al., 2013). A recent study also confirmed reduced medial prefrontal cortex activation for social abstract unimodal gestures in SSD patients (He et al., 2021). Furthermore, the STS, known for its role in multimodal sensory integration, was functionally disconnected from the IFG particularly for metaphoric gestures in patients (Straube, Green, et al., 2014). These abnormalities could contribute to impaired processing of abstract and metaphoric information.

Apart from that, our data confirm that the **temporal lobe** is similarly engaged in patients and controls for the perception of metaphoric gestures (Hypothesis C.a.). This common activation suggests that at least some neural mechanisms relevant for abstractness-processing are unimpaired in patients with SSD, providing the basis for successful interventions, such as gesture training (Riedl et al., 2020), transcranial magnetic stimulation (Walther et al., 2019), or tDCS (Schülke & Straube, 2019) (see chapter 5.5.).

The increased engagement of **cerebellar structures** for abstract stimuli in patients was an unexpected finding. The cerebellum plays an important role in language processing, possibly by predicting upcoming semantic content (D'Mello et al., 2017; Geva et al., 2021; Lesage et al., 2017). It was also shown to react when these predictions were erroneous (Lesage et al., 2017). Thus, it can be hypothesized that the high activation in SSD patients for abstract content reflects a compensatory mechanism for disrupted semantic processing in the IFG. Otherwise, it could be a reaction to frequent prediction errors for abstract semantic content, which might be more difficult to foresee for patients with concretism. However, these theories require further examination to unveil the function of the cerebellum in abstract speech-gesture processing.

### 5.3.1. The role of the IFG in speech and gesture

This study confirmed that the IFG has an important function in the processing of abstract speech and gesture combinations. However, the role of the IFG in semantic processing is very complex and not yet fully understood.

To begin with, it can be said that speech and gesture processing are closely related to each other. Both speech and gestures are processed in a **supramodal network** found in the left IFG and bilateral temporal lobes (Straube et al., 2012; Straube, He, et al., 2013; Xu et al., 2009). This relationship could be explained by the evolutionary development of language. Gentilucci and colleagues (2006) suggest that speech is a gestural system, as it is derived from manual communicative gestures. They argue that the perception of action (and gestures) has a lot of similarities with the language processing system (Gentilucci & Corballis, 2006; Gentilucci & Dalla Volta, 2008; Rizzolatti, 2005; Rizzolatti & Arbib, 1998). Interestingly, action perception and language share the engagement of the IFG. This supports the idea that both speech and gesture are processed by a common neural network derived from motor perception. Followingly, it can be inferred that IFG dysfunctions associated with language disturbances can have effects on gesture perception and production in SSD.

Furthermore, the IFG is part of the left-hemispheric **"praxis network"**, which was held accountable for apraxia in stroke patients based on lesion studies (Bohlhalter et al., 2009; Lesourd et al., 2018). This proves the importance of the region not only for the perception of action (and gestures), but also for their execution. The gesture deficits reported in schizophrenia patients do indeed display features of apraxia (Walther et al., 2020); a link to disturbed connectivity between the bilateral IFG is suspected (Viher et al., 2020).

Being a cortical region involved in the perception as well as in the production of action and language, the IFG constitutes a **junction point for multisensory input**. It is regarded as an integrational hub for multimodal semantic information, such as co-speech gestures (Dick et al. 2014, He et al. 2018). For example, the IFG shows higher activation when speech is accompanied by gestures than when it is not, especially when the gesture adds disambiguating, communicative information (Dick, Mok, et al., 2014; He et al., 2018; Straube et al., 2012).

Structural or functional aberrations of the IFG could therefore impede speech and gesture perception individually, as well as their integration and their production.

However, these approaches do not yet explain why in SSD patients, abstract semantic processing is disturbed whereas concrete semantic processing is often intact (Straube, Green, et al., 2013, 2014).

A model which attempts to explain the differential processing of abstract speech and gestures is the **semantic unification theory** (introduced in chapter 2.4.) (Hagoort et al., 2009; Willems et al., 2009). The increased integration load contained in metaphoric co-speech gestures requires sufficient activation of the IFG for successful unification of the information streams to a novel representation (Hagoort et al., 2009; Straube et al., 2011; Willems et al., 2009). However, connectivity between the temporal lobe and the IFG is disturbed in SSD (Straube, Green, et al., 2014). As this is accompanied by structural abnormalities (Stegmayer, Bohlhalter, et al., 2016, 2016; Viher et al., 2018), it can be speculated that the two-stepped integration of co-verbal gestures is interrupted after temporal processing before proceeding to the IFG (He et al., 2018).

It is therefore possible that semantic unification is defective in patients, with metaphoric gestures being especially vulnerable. Our study results encourage this theory and call for further examination of IFG dysfunctions in SSD patients for the development of targeted therapy options (see chapter 6.4.).

### 5.3.2. Temporal lobe integrity in SSD

Our study sample revealed common activation of the MTG and STG in both groups for abstract as opposed to concrete stimuli. This suggests that metaphoric speech-gesture processing is not completely impaired but partially functioning in SSD, which may build the necessary foundation for - e.g., training- or stimulation-induced - improvement. This is consistent with our hypothesis, as some studies have already shown that partial temporal networks are unimpaired in SSD (Straube, Green, et al., 2013; Wroblewski et al., 2019).

A large body of evidence confirms the STG/MTG's role in language perception (Andric et al., 2013; Kircher et al., 2007; Mashal et al., 2014; Rossetti et al., 2018; Skipper-Kallal et al., 2015; Straube et al., 2011; Straube, He, et al., 2013; Thoma & Daum, 2006) and the STS' function as an audiovisual integration site (Beauchamp et al., 2004; Calvert, 2001; Fitzhugh et al., 2019; Hein et al., 2007; Lotze et al., 2006; Pekkola et al., 2006; Straube et al., 2018).

Following up on the **semantic unification theory**, the intact temporal engagement may explain why in a number of studies, processing of iconic speech-gesture pairs was unimpaired in SSD (Straube, Green, et al., 2013, 2014). If it is the connectivity between the STS and IFG that is disturbed in SSD (Straube, Green, et al., 2014), we can hypothesize that the **two-stepped integration process for gesture and speech** is interrupted after the first step in the temporal lobe and can not proceed in the IFG (He et al., 2018). As a consequence, abstract semantic processing takes place in the temporal lobe, but fails to reach the IFG.

However, findings concerning the **integrity of temporal areas** in SSD are inconsistent. Straube and colleagues found reduced activation in the MTG only for metaphoric, but not for iconic gestures (Straube, Green, et al., 2014). Gesture performance and functional connectivity of the bilateral STG was correlated in healthy controls; this was not the case in schizophrenia patients, but connectivity was reduced (Wüthrich, Viher, et al., 2020). Even the connectivity between the left STS and the MTG, an essential language pathway, was decreased (Wroblewski et al., 2019). Aberrations of STS activity in schizophrenia have been previously associated with audiovisual integration (Szycik et al., 2009) and gesture imitation (Thakkar et al., 2014). Besides these functional deficits, reduced cortical thickness was detected in gesturally impaired schizophrenia patients in the STG and MTG (Viher et al., 2018).

This being said, we suggest that temporal lobe activation for abstract speech-gesture combinations is intact in SSD patients. It can be hypothesized that our results differ from previous investigations because of the additional semantic task. However, we propose that the observed **functional integrity of the temporal lobes** may be a prerequisite for successful therapeutic interventions.

Overall, it can be said that in order to fully understand the functional signature of abstract and metaphoric speech and gesture processing in SSD, more focused research is indispensable.

## 5.4. Limitations

In our trial, we investigated task-dependent BOLD-responses in schizophrenia spectrum disorder and healthy controls. Although we did not perform a one-by-one matching, sociological parameters such as age, gender and education were balanced in our study samples. Further, patients were moderately ill (mean SAPS 19.74 (SD 19.1); mean SANS 23.05 (SD 21.2)) and received individual medication. Medication effects can thus not be ruled out. Patient samples displaying stronger symptoms in certain categories (e.g., formal thought disorder, negative symptoms) could yield different effects as seen in Nagels (2019), where patients with pronounced formal thought disorder had reduced mismatch detection performance in the abstract category. Also, patients were not specifically tested for psychiatric diagnoses other than SSD.

Furthermore, intelligence and semantic processing are tightly intertwined, so that differences caused by cognition are not precluded, although patients and controls were matched for education.

Age was included as a covariate of no interest and no statistical correlation was found with our main results. Since the groups were matched, effects evoked by the age range are unlikely (see appendix, Supplementary table 4) (Cuevas et al., 2021).

In both groups, more male than female participants were included. Future investigations should aim for an equal representation of the sexes. However, groups were matched for sex, so that no relevant effects on our results are expected (see appendix, Supplementary table 3).

Although the number of left-handed subjects was not balanced across groups, no difference in activation was found whether they were included in the analysis or not (see appendix, Supplementary table 2).

Also, fMRI-compatibility was required for participation. Because equal numbers of patients and controls had to be excluded from the analysis based on our data quality criteria (Power et al., 2014, 2015; Soares et al., 2016; Wilke, 2014), we do not expect the selection to have influenced our results. However, the sample might not realistically mirror the general patient population.

Four gesture-speech video conditions were presented in our fMRI paradigm: abstract related, abstract unrelated, concrete related and concrete unrelated. We refrained from introducing a unimodal control condition because we were not particularly interested in modality-dependent effects. This allowed for an investigation of naturalistic communication, where gesture and speech usually coincide. It is not possible to distinguish task effects from purely perceptive effects since we did not implement a non-task control condition. Furthermore, the detection rate was utilized as an indirect measure for gesture-speech recognition, although it is debatable to what extent this parameter reflects semantic comprehension of gestures and/or speech.

## 5.5. Implications and outlook

SSD is a highly heterogeneous illness not only in terms of clinical presentation, but also on a neural level. As discussed in the preceding chapters, a plethora of behavioral and neuroimaging data point to a variety of neural dysfunctions that may affect patients' lives. Most likely, the interaction of multiple factors (e.g., genetic, neurobiological, developmental, socioeconomic, psychological) accounts for the observed symptoms and impairments, varying from one individual to the other. In the context of this study, only a few of these possible contributing mechanisms could be discussed. This underlines the importance of further research in the field of SSD, but also psychiatric disease in general, going beyond diagnostic labels and focussing on individual clinical and neuroscientific presentation, as suggested by the RDoC initiative (Walter, 2017). This approach might help to better understand how certain symptoms are linked to neuroscientific findings and pave the way towards symptom-specific diagnosis and treatment.

Impairment of speech and gesture production and perception are a stable feature in the course of disease of SSD patients and affect symptoms and progress (Kircher & Gauggel, 2008; Stegmayer, Moor, et al., 2016; Walther et al., 2016). We chose a broad patient sample from the schizophrenia spectrum for a comprehensive view on possible pathomechanisms. Interestingly, the ability to correctly identify related and unrelated speech-gesture combinations was reduced in the patient group, with corresponding decreased activation of the SMA and ACC and frontotemporal hyperactivation. The perception of abstract stimuli was associated with an IFG dysfunction. Our results endorse the theory that semantic recognition is in fact related to cortical dysfunctions in SSD patients. Some investigators go as far as to promote language and gesture performance parameters or functional characteristics as markers for disease and progress (Bagewadi et al., 2018; de Boer et al., 2020; Jamadar et al., 2013; Walther et al., 2016). With further underpinning studies, the speech-gesture mismatch detection task and its neural correlates could also be considered for this purpose. More intriguingly, if these parameters could be implemented across diagnostic groups, individualized treatment options that excel current standards could be offered.

So far, gesture impairment is neither diagnosed nor treated in a standardized manner, however, experimental therapies delivered promising results in recent years.

The aforementioned tDCS study by Schülke and Straube (Schülke & Straube, 2019) succeeded in improving the relatedness assessment performance for speech-gesture combinations in SSD patients. They showed a significant effect for left frontal inhibitory stimulation, a finding that can now be supported by our neural data. However, we did not only find overactivation of the left frontal cortex, but also hypoactivation of the SMA and ACC. Vukovic and colleagues (2017) revealed that repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex improved response times in a semantic judgment task for abstract items but slowed them down for concrete items in healthy study participants. Not only does this demonstrate how neurostimulation of the motor system can have an active influence on semantic comprehension, putting forward the action-perception model of language. It does also show once again that abstract and concrete stimuli are distinctly processed and hence deserve differentiated observation. Further research is needed to prove the effects of IFG stimulation on abstractness processing in SSD. Walther and colleagues (Walther et al., 2019) applied rTMS to schizophrenia patients and achieved improvement of gesture performance by inhibitory stimulation of the right IPL. This result indicates that gesture impairment in SSD can be modified by interventional therapies. The fact that the patient group showed partially intact neural activation for abstract > concrete (temporal lobe) and unrelated > related (rostral SMA) conditions shows that there is a functioning basis on which interventions can build on.

A new take on the treatment of speech and gesture therapies was introduced by Riedl and colleagues (Riedl et al., 2020). By implementing a speech-gesture training integrating tasks of gesture perception, relatedness assessment, imitation, and production along with self-observation and reflection assignments, the authors hope to ameliorate speech-gesture processing on a neural basis. The multimodal personal training is also expected to improve day-to-day life communication skills and social functioning. First results even showed an increase in subjective quality of life correlated with temporal BOLD signal activation for abstract stimuli (Riedl et al., 2021). This result further supports the need for a more multimodal and personalized take on SSD therapy.

Taken together, our results are well underpinned by previous research findings while still offering new perspectives on the processing of abstract and unrelated speech-gesture combinations. Stimulation of the IFG, SMA and ACC should be considered for future investigations of speech and gesture processing in SSD. The speech-gesture mismatch detection task could be of special interest as a performance marker for speech-gesture training.

## 5.6. Conclusion

With this study, we demonstrated that SSD patients have behavioral and neural impairments during mismatch detection of abstract and concrete speech-gesture combinations.

On the one hand, patients made more errors than healthy controls when discriminating between related and unrelated speech-gesture pairs. Their performance was reduced irrespective of abstractness, pointing to a generalized impairment. Dysfunctions of the SMA could contribute to disrupted semantic judgment by perturbing the facilitation of comprehension by the motor system. Malfunction of the ACC could either be a consequence of reduced comprehension or lead to impaired conflict processing. Also, left frontotemporal hyperactivation could be a sign of an increased processing demand.

On the other hand, we found a processing deficit for abstract speech-gesture combinations in SSD patients. The discovered IFG dysfunction is consistent with previous study results and may represent another neural correlate of impaired semantic recognition in patients.

Altogether, this study showed that an in-scanner speech-gesture mismatch detection task can unmask functional aberrations in SSD patients. Along with earlier data corroborating the tight association between neural dysfunctions, communication impairment and negative symptoms, it can be assumed that optimization or manipulation of either factor could engender generalized improvement of the other factors. Our results confirming the role of neural dysfunctions on task performance add to the neuroscientific groundwork that enables further multimodal therapy investigations (Riedl et al., 2020). First evidence for the positive effect of brain stimulation on mismatch detection rates (Schülke & Straube, 2017, 2019) and gesture performance (Walther et al., 2019) already exists.

# 6. Summaries

## 6.1. Summary (English)

**Background:** Patients suffering from schizophrenia spectrum disorders experience the grave effects of their illness on various facets of their daily lives.

Previous investigations have shown that schizophrenia spectrum disorder patients have deficits in the perception and recognition of speech accompanied by gestures. In particular, they struggle to differentiate between related and unrelated speech-gesture combinations. Also, patients have considerable difficulties in understanding and processing abstract semantic information. A key region in the integration of speech and gesture is the inferior frontal gyrus embedded in a frontotemporal network, however, it is unclear which neural mechanisms contribute to defective mismatch and abstractness perception during the mismatch detection task.

**Objective:** This study aimed to investigate the neural underpinnings of impaired speech-gesture mismatch detection and abstract semantic processing in schizophrenia spectrum disorder patients and to identify relevant dysfunctional brain areas.

**Methods:** A novel mismatch-detection fMRI paradigm was implemented manipulating speech-gesture abstractness (abstract/concrete) and relatedness (related/unrelated). During fMRI data acquisition, 42 patients (schizophrenia, schizoaffective disorder or other non-organic psychotic disorder [ICD-10: F20, F25, F28; DSM-IV: 295.X]) and 36 healthy controls were presented with short video clips of an actor reciting abstract or concrete sentences accompanied by either a semantically related or unrelated gesture. Participants indicated via button press whether they perceived each gesture as matching the speech content or not.

We compared task performances across groups and semantic context (abstract/concrete) using the detection rate from Signal Detection Theory by repeated-measures ANOVA.

For the functional MRI data, an event-related design was chosen to measure the hemodynamic responses to each presented video. The data were loaded into a flexible-factorial analysis in a 2 x 2 x 2 design (group x abstractness x relatedness).

Between-group conjunctions and group differences were respectively calculated for the contrasts unrelated > related and abstract > concrete in whole-brain analyses.

**Results:** Speech-gesture mismatch detection performance was significantly impaired in patients compared to controls, irrespective of abstractness. fMRI data analysis revealed that patients exhibited reduced engagement of the right supplementary motor area and bilateral anterior cingulate cortices for unrelated > related stimuli. A rostral part of the supplementary motor area was equally activated in both groups. In contrast, we found frontotemporal hyperactivation in patients for the same contrast. Furthermore, patients showed lower activation in bilateral frontal areas including the inferior frontal gyrus for all abstract > concrete speech-gesture pairs. The temporal lobe, however, was engaged in both groups equally for this contrast.

**Discussion:** In this study, we found evidence for impaired gesture-speech relatedness judgment in schizophrenia spectrum disorders. This was accompanied by dysfunctions of the supplementary motor area and the anterior cingulate cortices, possibly reflecting reduced facilitation of comprehension and defective error processing for unrelated speech-gesture combinations. The frontotemporal hyperactivation may represent an increased processing effort to compensate for the dysfunction. In addition, our data confirmed the conjecture of an inferior frontal gyrus dysfunction contributing to impaired processing of abstract semantic stimuli. Partially intact processing was discovered in a rostral part of the supplementary motor area for mismatches, and in the temporal lobes for abstract stimuli. These findings suggest that semantic processing in schizophrenia spectrum disorders is not completely dysfunctional, but that there is a functioning basis on which therapeutic measures can build on.

**Conclusion:** We provide first evidence that impaired speech-gesture mismatch detection in schizophrenia spectrum disorders could be the result of dysfunctional activation of the supplementary motor area and anterior cingulate cortex. Failure to activate the left inferior frontal gyrus disrupts the integration of abstract speech-gesture combinations in particular. Future investigations should focus on brain-stimulation of these regions to improve communication and social functioning in schizophrenia spectrum disorders.

## 6.2. Zusammenfassung (deutsch)

**Hintergrund:** Patient*innen, die an einer Schizophrenie-Spektrum-Störung leiden, erleben die schwerwiegenden Auswirkungen ihrer Krankheit auf verschiedene Alltagsbereiche. Bisherige Untersuchungen zeigten, dass solche Patient*innen Defizite bei der Wahrnehmung und Erkennung von Sprache in Verbindung mit Gesten haben. Insbesondere fällt es ihnen schwer, zwischen passenden und nicht passenden Sprach-Gestik-Kombinationen (Matches und Mismatches) zu unterscheiden. Desweiteren haben die Patient*innen erhebliche Schwierigkeiten, abstrakte semantische Informationen zu verstehen und neural zu verarbeiten. Eine Schlüsselrolle bei der Integration von Sprache und Gesten spielt der Gyrus frontalis inferior als Teil des frontotemporalen Netzwerks. Es ist jedoch unklar, welche neuronalen Mechanismen zu einer gestörten Wahrnehmung von Mismatches und Abstraktheit während der Passungs-Bewertungs-Aufgabe beitragen.

**Ziel:** Diese Studie versucht, die neuronalen Hintergründe der gestörten Sprach-Gestik-Mismatch-Detektion sowie der fehlerhaften Verarbeitung abstrakter semantischer Information zu beleuchten. Dabei sollen die dysfunktionalen Hirnareale identifiziert und untersucht werden.

**Methoden:** Für diese Studie wurde ein neuartiges Paradigma angewandt, bei dem funktionelle MRT-Messungen durchgeführt wurden, während Probanden eine Sprach-Gestik-Passungs-Bewertungs-Aufgabe bearbeiteten. 42 Patient*innen (Schizophrenie, schizoaffektive Störung oder andere nicht-organische psychotische Störung [ICD-10: F20, F25, F28; DSM-IV: 295.X]) und 36 gesunden Kontrollproband*innen wurden kurze Videoclips gezeigt, in denen ein Schauspieler Sätze mit abstraktem oder konkretem Inhalt spricht und dabei entweder semantisch passende oder nicht-passende Gesten durchführt. Die Teilnehmer*innen wurden gebeten, per Tastendruck anzuzeigen, ob sie die Gesten als passend zur gesprochenen Sprache empfanden oder nicht.

Die Detektionsleistung zwischen passenden und nicht passenden Gesten wurde in Anlehnung an die Signaldetektionstheorie per Messwiederholungs-ANOVA zwischen Gruppen und semantischen Kontexten (abstrakt/konkret) verglichen. Funktionelle MRT-Daten wurden im Rahmen eines ereigniskorrelierten Designs gesammelt, um die hämodynamische Antwort auf jedes gezeigte Video zu erfassen. Die Daten

wurden anschließend in eine flexible Faktorenanalyse in einem 2 x 2 x 2 - Design (Gruppe x Abstraktheit x Passung) geladen. Für die Kontraste unpassend > passend und abstrakt > konkret wurden jeweils die Zwischengruppenkonjunktionen und -differenzen in Gesamthirnanalysen berechnet.

**Ergebnisse:** Die Sprach-Gestik-Mismatch-Detektionsleistung war bei Patient*innen im Vergleich zu den Kontrollen signifikant verringert, unabhängig von der Abstraktheit. Die fMRT-Analyse zeigte, dass Patient*innen für unpassende > passende Stimuli weniger Aktivität im rechten supplementär-motorischen Kortex und im beidseitigen anterioren cingulären Kortex aufweisen. Ein rostraler Teil des supplementär-motorischen Kortex war genauso aktiv wie bei Kontrollproband*innen. Gleichzeitig fanden wir frontotemporale Hyperaktivität bei Patient*innen für diesen Kontrast. Weiterhin wurde bei Patient*innen im Vergleich zu Kontrollen reduzierte bilateral frontale Aktivität, insbesondere auch im Gyrus frontalis inferior, für abstrakte > konkrete Sprach-Gestik-Paare festgestellt. Der Temporallappen, im Gegensatz, war für diesen Kontrast in beiden Gruppen gleichermaßen aktiv.

Diskussion

In dieser Studie fanden wir Hinweise für eine gestörte Sprach-Gestik-Passungs-Bewertungsfähigkeit bei Patient*innen mit einer Schizophrenie-Spektrum-Störung. Begleitet war dies von Dysfunktionen des supplementär-motorischen Kortex und des anterioren cingulären Kortex, was möglicherweise Ausdruck verringerter Bahnung von semantischem Verständnis und geschädigter Fehlerverarbeitung für unpassende Sprach-Gestik-Kombinationen ist. Die frontotemporale Überaktivierung könnte eine kompensatorisch erhöhte Anstrengung für die Verarbeitung in einem dysfunktionalen System reflektieren. Zusätzlich bestärken unsere Daten die Auffassung, dass Störungen des Gyrus frontalis inferior zu einer Beeinträchtigung der Verarbeitung abstrakter semantischer Stimuli beitragen. Die teilweise intakte Funktionalität im rostralen supplementär-motorischen Kortex für Mismatches und im Temporallappen für abstrakte Stimuli sprechen dafür, dass die semantische Verarbeitung bei Patient*innen nicht vollständig dysfunktional ist. Diese funktionierenden Anteile könnten als Ansatzpunkte für therapeutische Maßnahmen dienen, um Verbesserungen herbeizurufen.

**Schlussfolgerung:** Wir liefern erste Belege dafür, dass die gestörte Sprach-Gestik-Mismatch-Detektionsfähigkeit das Resultat von Fehlaktivierungen der supplementär-motorischen und anterior cingulären Kortizes sein könnte. Außerdem wird vermutet, dass die fehlerhafte Funktion des IFG die korrekte Integration von abstrakten Sprach-Gestik-Kombinationen erschwert. Zukünftige Untersuchungen sollten sich auf hirnstimulative Verfahren fokussieren, die diese dysfunktionalen Areale beeinflussen, um Kommunikationsfähigkeit und soziale Funktionalität bei Patient*innen mit Schizophrenie-Spektrum-Störung zu verbessern.

# 7. References

Adamczyk, P., Jáni, M., Ligeza, T. S., Płonka, O., Błądziński, P., & Wyczesany, M. (2021). On the Role of Bilateral Brain Hypofunction and Abnormal Lateralization of Cortical Information Flow as Neural Underpinnings of Conventional Metaphor Processing Impairment in Schizophrenia: An fMRI and EEG Study. *Brain Topography*, *34*(4), 537–554. https://doi.org/10.1007/s10548-021-00849-x

Alario, F.-X., Chainay, H., Lehericy, S., & Cohen, L. (2006). The role of the supplementary motor area (SMA) in word production. *Brain Research*, *1076*(1), 129–143. https://doi.org/10.1016/j.brainres.2005.11.104

Álvarez-Jiménez, M., Gleeson, J. F., Henry, L. P., Harrigan, S. M., Harris, M. G., Killackey, E., Bendall, S., Amminger, G. P., Yung, A. R., Herrman, H., Jackson, H. J., & McGorry, P. D. (2012). Road to full recovery: Longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. *Psychological Medicine*, *42*(3), 595–606. https://doi.org/10.1017/S0033291711001504

Andreasen, N. (1984a). *Scale for the assessment of negative symptoms (SANS)*. University of Iowa Press.

Andreasen, N. (1984b). *The scale for the assessment of positive symptoms*. University of Iowa Press.

Andreasen, N. C., Calage, C. A., & O'Leary, D. S. (2008). Theory of Mind and Schizophrenia: A Positron Emission Tomography Study of Medication-Free Patients. *Schizophrenia Bulletin*, *34*(4), 708–719. https://doi.org/10.1093/schbul/sbn034

Andric, M., & Small, S. L. (2012). Gesture's Neural Language. *Frontiers in Psychology*, *3*. https://doi.org/10.3389/fpsyg.2012.00099

Andric, M., Solodkin, A., Buccino, G., Goldin-Meadow, S., Rizzolatti, G., & Small, S. L. (2013). Brain Function Overlaps When People Observe Emblems, Speech, and

Grasping. *Neuropsychologia*, *51*(8). https://doi.org/10.1016/j.neuropsychologia.2013.03.022

Arcuri, S. M., Broome, M. R., Giampietro, V., Amaro, E., Kircher, T. T. J., Williams, S. C. R., Andrew, C. M., Brammer, M., Morris, R. G., & McGuire, P. K. (2012). Faulty Suppression of Irrelevant Material in Patients with Thought Disorder Linked to Attenuated Frontotemporal Activation. *Schizophrenia Research and Treatment*, *2012*. https://doi.org/10.1155/2012/176290

Bagewadi, V. I., Mehta, U. M., Naik, S. S., Govindaraj, R., Varambally, S., Arumugham, S. S., Naveen Kumar, C., & Thirthalli, J. (2018). Diminished modulation of motor cortical reactivity during context-based action observation in schizophrenia. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2018.07.043

Bailey, A. J., Moussa-Tooks, A. B., Klein, S. D., Sponheim, S. R., & Hetrick, W. P. (2021). The Sensory Gating Inventory-Brief. *Schizophrenia Bulletin Open*, *2*(1), sgab019. https://doi.org/10.1093/schizbullopen/sgab019

Bambini, V., Arcara, G., Bosinelli, F., Buonocore, M., Bechi, M., Cavallaro, R., & Bosia, M. (2020). A leopard cannot change its spots: A novel pragmatic account of concretism in schizophrenia. *Neuropsychologia*, 45. https://doi.org/10.1016/j.neuropsychologia.2020.107332

Barch, D. M., Braver, T. S., Sabb, F. W., & Noll, D. C. (2000). Anterior cingulate and the monitoriing of response conflict: Evidence from an fMRI study of overt verb generation. *Journal of Cognitive Neuroscience*, *12*(2), 298–309. https://doi.org/10.1162/089892900562110

Barth, A., & Küfferle, B. (2001). Development of a proverb test for assessment of concrete thinking problems in schizophrenic patients. *Der Nervenarzt*, *72*(11), 853–858.

Bashir, U., & Feger. (2012, August 7). *Echo planar imaging | Radiology Reference Article | Radiopaedia.org*. Radiopaedia. https://radiopaedia.org/articles/echo-planar-imaging-1

Bates, M. E., & Lemay, E. P. (2004). The d2 Test of attention: Construct validity and extensions in scoring techniques. *Journal of the International Neuropsychological*

*Society: JINS*, *10*(3), 392–400. https://doi.org/10.1017/S135561770410307X

Beauchamp, M. S., Lee, K. E., Argall, B. D., & Martin, A. (2004). Integration of Auditory and Visual Information about Objects in Superior Temporal Sulcus. *Neuron*, *41*(5), 809–823. https://doi.org/10.1016/S0896-6273(04)00070-4

Becerril, K. E., Repovs, G., & Barch, D. M. (2011). Error processing network dynamics in schizophrenia. *NeuroImage*, *54*(2), 1495–1505. https://doi.org/10.1016/j.neuroimage.2010.09.046

Beeman, M. (1998). Coarse semantic coding and discourse comprehension. In *Right hemisphere language comprehension: Perspectives from cognitive neuroscience* (pp. 255–284). Lawrence Erlbaum Associates Publishers.

Beeman, M. J., & Chiarello, C. (1998). Complementary Right- and Left-Hemisphere Language Comprehension. *Current Directions in Psychological Science*, *7*(1), 2–8. https://doi.org/10.1111/1467-8721.ep11521805

Berndl, K., von Cranach, M., & Grüsser, O. J. (1986). Impairment of perception and recognition of faces, mimic expression and gestures in schizophrenic patients. *European Archives of Psychiatry and Neurological Sciences*, *235*(5), 282–291.

Bhati, M. T. (2013). Defining Psychosis: The Evolution of DSM-5 Schizophrenia Spectrum Disorders. *Current Psychiatry Reports*, *15*(11), 409. https://doi.org/10.1007/s11920-013-0409-9

Blackburn, H. L., & Benton, A. L. (1957). Revised administration and scoring of the Digit Span Test. *Journal of Consulting Psychology*, *21*(2), 139–143. https://doi.org/10.1037/h0047235

Bohlhalter, S., Hattori, N., Wheaton, L., Fridman, E., Shamim, E. A., Garraux, G., & Hallett, M. (2009). Gesture Subtype–Dependent Left Lateralization of Praxis Planning: An Event-Related fMRI Study. *Cerebral Cortex (New York, NY)*, *19*(6), 1256–1262. https://doi.org/10.1093/cercor/bhn168

Bosco, F. M., Berardinelli, L., & Parola, A. (2019). The Ability of Patients With Schizophrenia to Comprehend and Produce Sincere, Deceitful, and Ironic Communicative

Intentions: The Role of Theory of Mind and Executive Functions. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.00827

Bosco, F. M., Tirassa, M., & Gabbatore, I. (2018). Why Pragmatics and Theory of Mind Do Not (Completely) Overlap. *Frontiers in Psychology*, *9*, 1453. https://doi.org/10.3389/fpsyg.2018.01453

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences*, *8*(12), 539–546. https://doi.org/10.1016/j.tics.2004.10.003

Bowie, C. R., & Harvey, P. D. (2006). Administration and interpretation of the Trail Making Test. *Nature Protocols*, *1*(5), 2277–2281. https://doi.org/10.1038/nprot.2006.390

Bozikas, V., & Parlapani, E. (2016). Resilience in patients with psychotic disorder. *Psychiatrike = Psychiatriki*, *27*(1), 13–16.

Bracht, T., Schnell, S., Federspiel, A., Razavi, N., Horn, H., Strik, W., Wiest, R., Dierks, T., Müller, T. J., & Walther, S. (2013). Altered cortico-basal ganglia motor pathways reflect reduced volitional motor activity in schizophrenia. *Schizophrenia Research*, *143*(2–3), 269–276. https://doi.org/10.1016/j.schres.2012.12.004

Brackmann, N., Lau, S., Habermeyer, E., & Weiss, J. (2020). Konkretistische Denkstörungen als Indikator der Akuität bei Schizophrenieerkrankungen. *Psychiatrische Praxis*, *47*(1), 29–34. https://doi.org/10.1055/a-1026-0808

Bucci, S., Startup, M., Wynn, P., Heathcote, A., Baker, A., & Lewin, T. J. (2008). Referential delusions of communication and reality discrimination deficits in psychosis. *The British Journal of Clinical Psychology*, *47*(Pt 3), 323–334. https://doi.org/10.1348/014466508X280952

Buccino, G., Binkofski, F., Fink, G. R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R. J., Zilles, K., Rizzolatti, G., & Freund, H.-J. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: An fMRI study. *European Journal of Neuroscience*, *13*(2), 400–404. https://doi.org/10.1111/j.1460-9568.2001.01385.x

Buccino, G., Binkofski, F., & Riggio, L. (2004). The mirror neuron system and action recognition. *Brain and Language*, *89*(2), 370–376. https://doi.org/10.1016/S0093-934X(03)00356-0

Calvert, G. A. (2001). Crossmodal Processing in the Human Brain: Insights from Functional Neuroimaging Studies. *Cerebral Cortex*, *11*(12), 1110–1123. https://doi.org/10.1093/cercor/11.12.1110

Chakrabarty, M., Sarkar, S., Chatterjee, A., Ghosal, M., Guha, P., & Deogaonkar, M. (2014). Metaphor comprehension deficit in schizophrenia with reference to the hypothesis of abnormal lateralization and right hemisphere dysfunction. *Language Sciences*, *44*, 1–14. https://doi.org/10.1016/j.langsci.2014.01.002

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., McGrath, J. J., & Whiteford, H. A. (2018). Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophrenia Bulletin*, *44*(6), 1195–1203. https://doi.org/10.1093/schbul/sby058

Chen, J., Wensing, T., Hoffstaedter, F., Cieslik, E. C., Müller, V. I., Patil, K. R., Aleman, A., Derntl, B., Gruber, O., Jardri, R., Kogler, L., Sommer, I. E., Eickhoff, S. B., & Nickl-Jockschat, T. (2021). Neurobiological substrates of the positive formal thought disorder in schizophrenia revealed by seed connectome-based predictive modeling. *NeuroImage: Clinical*, *30*, 102666. https://doi.org/10.1016/j.nicl.2021.102666

Chen, X., Scangos, K. W., & Stuphorn, V. (2010). Supplementary motor area exerts proactive and reactive control of arm movements. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(44), 14657–14675. https://doi.org/10.1523/JNEUROSCI.2669-10.2010

Colle, L., Angeleri, R., Vallana, M., Sacco, K., Bara, B. G., & Bosco, F. M. (2013). Understanding the communicative impairments in schizophrenia: A preliminary study. *Journal of Communication Disorders*, *46*(3), 294–308. https://doi.org/10.1016/j.jcomdis.2013.01.003

Collins, A. M., & Loftus, E. F. (1975). A spreading-activation theory of semantic processing. *Psychological Review*, *82*(6), 407–428. https://doi.org/10.1037/0033-295X.82.6.407

Cuevas, P., He, Y., Billino, J., Kozasa, E., & Straube, B. (2021). Age-related effects on the neural processing of semantic complexity in a continuous narrative: Modulation by gestures already present in young to middle-aged adults. *Neuropsychologia*, *151*, 107725. https://doi.org/10.1016/j.neuropsychologia.2020.107725

de Boer, J. N., Brederoo, S. G., Voppel, A. E., & Sommer, I. E. C. (2020). Anomalies in language as a biomarker for schizophrenia. *Current Opinion in Psychiatry*, *Publish Ahead of Print*. https://doi.org/10.1097/YCO.0000000000000595

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: Evidence from event-related fMRI studies. *Experimental Brain Research*, *133*(1), 3–11. https://doi.org/10.1007/s002210000395

DGPPN e.V. (2019). *S3-Leitlinie Schizophrenie. Langfassung*. https://www.awmf.org/leitlinien/detail/ll/038-009.html

Dick, A. S., Bernal, B., & Tremblay, P. (2014). The language connectome: New pathways, new concepts. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *20*(5), 453–467. https://doi.org/10.1177/1073858413513502

Dick, A. S., Mok, E. H., Beharelle, A. R., Goldin-Meadow, S., & Small, S. L. (2014). Frontal and temporal contributions to understanding the iconic co-speech gestures that accompany speech. *Human Brain Mapping*, *35*(3), 900–917. https://doi.org/10.1002/hbm.22222

D'Mello, A. M., Turkeltaub, P. E., & Stoodley, C. J. (2017). Cerebellar tDCS Modulates Neural Circuits during Semantic Prediction: A Combined tDCS-fMRI Study. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *37*(6), 1604–1613. https://doi.org/10.1523/JNEUROSCI.2818-16.2017

Donati, F. L., Kaskie, R., Reis, C. C., D'Agostino, A., Casali, A. G., & Ferrarelli, F. (2021). Reduced TMS-evoked fast oscillations in the motor cortex predict the severity of positive symptoms in first-episode psychosis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *111*, 110387.

https://doi.org/10.1016/j.pnpbp.2021.110387

Du, Y., Buchsbaum, B. R., Grady, C. L., & Alain, C. (2016). Increased activity in frontal motor cortex compensates impaired speech perception in older adults. *Nature Communications*, *7*. https://doi.org/10.1038/ncomms12241

Dutschke, L. L., Stegmayer, K., Ramseyer, F., Bohlhalter, S., Vanbellingen, T., Strik, W., & Walther, S. (2017). Gesture impairments in schizophrenia are linked to increased movement and prolonged motor planning and execution. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2017.07.012

Ellis, A. W., & Young, A. W. (2013). *Human Cognitive Neuropsychology: A Textbook With Readings*. Psychology Press.

Enticott, P. G., Hoy, K. E., Herring, S. E., Johnston, P. J., Daskalakis, Z. J., & Fitzgerald, P. B. (2008). Reduced motor facilitation during action observation in schizophrenia: A mirror neuron deficit? *Schizophrenia Research*, *102*(1), 116–121. https://doi.org/10.1016/j.schres.2008.04.001

Erickson, M. A., Hahn, B., Kiat, J. E., Alliende, L. M., Luck, S. J., & Gold, J. M. (2021). Neural basis of the visual working memory deficit in schizophrenia: Merging evidence from fMRI and EEG. *Schizophrenia Research*, *236*, 61–68. https://doi.org/10.1016/j.schres.2021.07.039

Fabbri-Destro, M., Avanzini, P., De Stefani, E., Innocenti, A., Campi, C., & Gentilucci, M. (2015). Interaction Between Words and Symbolic Gestures as Revealed By N400. *Brain Topography*, *28*(4), 591–605. https://doi.org/10.1007/s10548-014-0392-4

Fitzhugh, M. C., Whitehead, P. S., Johnson, L., Cai, J. M., Baxter, L. C., & Rogalsky, C. (2019). A functional MRI investigation of crossmodal interference in an audiovisual Stroop task. *PLoS ONE*, *14*(1). https://doi.org/10.1371/journal.pone.0210736

Fitzsimmons, J., Kubicki, M., & Shenton, M. E. (2013). Review of functional and anatomical brain connectivity findings in schizophrenia. *Current Opinion in Psychiatry*, *26*(2), 172–187. https://doi.org/10.1097/YCO.0b013e32835d9e6a

Galderisi, S., Mucci, A., Buchanan, R. W., & Arango, C. (2018). Negative symptoms of schizophrenia: New developments and unanswered research questions. *The Lancet Psychiatry*, *5*(8), 664–677. https://doi.org/10.1016/S2215-0366(18)30050-6

Galderisi, S., Rossi, A., Rocca, P., Bertolino, A., Mucci, A., Bucci, P., Rucci, P., Gibertoni, D., Aguglia, E., Amore, M., Bellomo, A., Biondi, M., Brugnoli, R., Dell'Osso, L., De Ronchi, D., Di Emidio, G., Di Giannantonio, M., Fagiolini, A., Marchesi, C., … Italian Network For Research on Psychoses. (2014). The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *13*(3), 275–287. https://doi.org/10.1002/wps.20167

Gavilán Ibáñez, J. M., & García-Albea Ristol, J. E. (2013). Theory of mind and language comprehension in schizophrenia. *Psicothema*, *25*(4), 440–445. https://doi.org/10.7334/psicothema2012.357

Gentilucci, M., & Corballis, M. (2006). *From manual gesture to speech: A gradual transition* (Vol. 30). https://doi.org/10.1016/j.neubiorev.2006.02.004

Gentilucci, M., & Dalla Volta, R. (2008). Spoken language and arm gestures are controlled by the same motor control system. *Quarterly Journal of Experimental Psychology (2006)*, *61*(6), 944–957. https://doi.org/10.1080/17470210701625683

Gernsbacher, M. A., Tallent, K. A., & Bolliger, C. M. (1999). Disordered discourse in schizophrenia described by the Structure Building Framework. *Discourse Studies*, *1*(3), 355–372. https://doi.org/10.1177/1461445699001003004

Geva, S., Schneider, L. M., Roberts, S., Green, D. W., & Price, C. J. (2021). The Effect of Focal Damage to the Right Medial Posterior Cerebellum on Word and Sentence Comprehension and Production. *Frontiers in Human Neuroscience*, *15*, 664650. https://doi.org/10.3389/fnhum.2021.664650

Giora, R. (2002). Literal vs. figurative language: Different or equal? *Journal of Pragmatics*, *34*(4), 487–506. https://doi.org/10.1016/S0378-2166(01)00045-5

Goldin-Meadow, S. (2015). From action to abstraction: Gesture as a mechanism of change. *Developmental Review : DR*, *38*, 167–184. https://doi.org/10.1016/j.dr.2015.07.007

Goldin-Meadow, S. (2017). Using our hands to change our minds. *Wiley Interdisciplinary Reviews. Cognitive Science*, *8*(1–2). https://doi.org/10.1002/wcs.1368

Goldin-Meadow, S., & Alibali, M. W. (2013). Gesture's role in speaking, learning, and creating language. *Annual Review of Psychology*, *64*, 257–283. https://doi.org/10.1146/annurev-psych-113011-143802

Green, A., Straube, B., Weis, S., Jansen, A., Willmes, K., Konrad, K., & Kircher, T. (2009). Neural integration of iconic and unrelated coverbal gestures: A functional MRI study. *Human Brain Mapping*, *30*(10), 3309–3324. https://doi.org/10.1002/hbm.20753

Hagoort, P., Baggio, G., & Willems, R. M. (2009). *Semantic unification*. MIT Press. https://pure.mpg.de/pubman/faces/ViewItemOverviewPage.jsp?itemId=item_64579

He, Y., Gebhardt, H., Steines, M., Sammer, G., Kircher, T., Nagels, A., & Straube, B. (2015). The EEG and fMRI signatures of neural integration: An investigation of meaningful gestures and corresponding speech. *Neuropsychologia*, *72*, 27–42. https://doi.org/10.1016/j.neuropsychologia.2015.04.018

He, Y., Steines, M., Sammer, G., Nagels, A., Kircher, T., & Straube, B. (2021). Modality-specific dysfunctional neural processing of social-abstract and non-social-concrete information in schizophrenia. *NeuroImage. Clinical*, *29*, 102568. https://doi.org/10.1016/j.nicl.2021.102568

He, Y., Steines, M., Sommer, J., Gebhardt, H., Nagels, A., Sammer, G., Kircher, T., & Straube, B. (2018). Spatial–temporal dynamics of gesture–speech integration: A simultaneous EEG-fMRI study. *Brain Structure and Function*, *223*(7), 3073–3089. https://doi.org/10.1007/s00429-018-1674-5

Hein, G., Doehrmann, O., Müller, N. G., Kaiser, J., Muckli, L., & Naumer, M. J. (2007). Object Familiarity and Semantic Congruency Modulate Responses in Cortical Audiovisual Integration Areas. *The Journal of Neuroscience*, *27*(30), 7881–7887. https://doi.org/10.1523/JNEUROSCI.1740-07.2007

Hertrich, I., Dietrich, S., & Ackermann, H. (2016). The role of the supplementary motor area for speech and language processing. *Neuroscience & Biobehavioral Reviews*, *68*, 602–610. https://doi.org/10.1016/j.neubiorev.2016.06.030

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, *8*(5), 393–402. https://doi.org/10.1038/nrn2113

Hinz, A., Michalski, D., Schwarz, R., & Herzberg, P. Y. (2007). The acquiescence effect in responding to a questionnaire. *GMS Psycho-Social Medicine*, *4*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2736523/

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *The Lancet. Psychiatry*, *4*(4), 295–301. https://doi.org/10.1016/S2215-0366(17)30078-0

Hodgson, J. C., & Hudson, J. M. (2018). Speech lateralization and motor control. *Progress in Brain Research*, *238*, 145–178. https://doi.org/10.1016/bs.pbr.2018.06.009

Holle, H., & Gunter, T. C. (2007). The Role of Iconic Gestures in Speech Disambiguation: ERP Evidence. *Journal of Cognitive Neuroscience*, *19*(7), 1175–1192. https://doi.org/10.1162/jocn.2007.19.7.1175

Holle, H., Gunter, T. C., Rüschemeyer, S.-A., Hennenlotter, A., & Iacoboni, M. (2008). Neural correlates of the processing of co-speech gestures. *NeuroImage*, *39*(4), 2010–2024. https://doi.org/10.1016/j.neuroimage.2007.10.055

Holle, H., Obleser, J., Rueschemeyer, S.-A., & Gunter, T. C. (2010). Integration of iconic gestures and speech in left superior temporal areas boosts speech comprehension under adverse listening conditions. *NeuroImage*, *49*(1), 875–884. https://doi.org/10.1016/j.neuroimage.2009.08.058

Iakimova, G., Passerieux, C., & Hardy-Baylé, M.-C. (2006). Interpretation of Ambiguous Idiomatic Statements in Schizophrenic and Depressive Patients. Evidence for Common and Differential Cognitive Patterns. *Psychopathology*, *39*(6), 277–285. https://doi.org/10.1159/000095732

Iakimova, G., Passerieux, C., Laurent, J.-P., & Hardy-Bayle, M.-C. (2005). ERPs of metaphoric, literal, and incongruous semantic processing in schizophrenia. *Psychophysiology*, *42*(4), 380–390. https://doi.org/10.1111/j.1469-8986.2005.00303.x

Iverson, J. M., & Goldin-Meadow, S. (2005). Gesture paves the way for language development. *Psychological Science*, *16*(5), 367–371. https://doi.org/10.1111/j.0956-7976.2005.01542.x

Jamadar, S. D., Pearlson, G. D., O'Neil, K. M., & Assaf, M. (2013). Semantic association fMRI impairments represent a potential schizophrenia biomarker. *Schizophrenia Research*, *145*(1), 20–26. https://doi.org/10.1016/j.schres.2012.12.029

Jardri, R., Pouchet, A., Pins, D., & Thomas, P. (2011). Cortical Activations During Auditory Verbal Hallucinations in Schizophrenia: A Coordinate-Based Meta-Analysis. *American Journal of Psychiatry*, *168*(1), 73–81. https://doi.org/10.1176/appi.ajp.2010.09101522

Karakuła, H., Krukow, P., Kalinowska, J., Stelmach, E., & Kowal-Popczak, A. (2013). Disintegration of social cognitive processes in schizophrenia. *Psychiatria Polska*, *47*(6), 1023–1039.

Kasai, K., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Onitsuka, T., Spencer, M. H., Yurgelun-Todd, D. A., Kikinis, R., Jolesz, F. A., & McCarley, R. W. (2003). Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: A longitudinal magnetic resonance imaging study. *Archives of General Psychiatry*, *60*(8), 766–775. https://doi.org/10.1001/archpsyc.60.8.766

Kasai, K., Yamada, H., Kamio, S., Nakagome, K., Iwanami, A., Fukuda, M., Yumoto, M., Itoh, K., Koshida, I., Abe, O., & Kato, N. (2003). Neuromagnetic correlates of impaired automatic categorical perception of speech sounds in schizophrenia. *Schizophrenia Research*, *59*(2–3), 159–172. https://doi.org/10.1016/s0920-9964(01)00382-6

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Kelly, S. D., Kravitz, C., & Hopkins, M. (2004). Neural correlates of bimodal speech and gesture comprehension. *Brain and Language*, *89*(1), 253–260. https://doi.org/10.1016/S0093-934X(03)00335-3

Kerns, J. G., Cohen, J. D., MacDonald, A. W., Johnson, M. K., Stenger, V. A., Aizenstein, H., & Carter, C. S. (2005). Decreased Conflict- and Error-Related Activity in the Anterior Cingulate Cortex in Subjects With Schizophrenia. *American Journal of Psychiatry*, *162*(10), 1833–1839. https://doi.org/10.1176/appi.ajp.162.10.1833

Ketteler, D., Theodoridou, A., Ketteler, S., & Jäger, M. (2012). High Order Linguistic Features Such as Ambiguity Processing as Relevant Diagnostic Markers for Schizophrenia. *Schizophrenia Research and Treatment*, *2012*. https://doi.org/10.1155/2012/825050

Kircher, T., & Gauggel, S. (Eds.). (2008). *Neuropsychologie der Schizophrenie: Symptome, Kognition, Gehirn ; mit 35 Tabellen*. Springer Medizin.

Kircher, T., Straube, B., Leube, D., Weis, S., Sachs, O., Willmes, K., Konrad, K., & Green, A. (2009). Neural interaction of speech and gesture: Differential activations of metaphoric co-verbal gestures. *Neuropsychologia*, *47*(1), 169–179. https://doi.org/10.1016/j.neuropsychologia.2008.08.009

Kircher, T. T. J., Leube, D. T., Erb, M., Grodd, W., & Rapp, A. M. (2007). Neural correlates of metaphor processing in schizophrenia. *NeuroImage*, *34*(1), 281–289. https://doi.org/10.1016/j.neuroimage.2006.08.044

Klauser, P., Baker, S. T., Cropley, V. L., Bousman, C., Fornito, A., Cocchi, L., Fullerton, J. M., Rasser, P., Schall, U., Henskens, F., Michie, P. T., Loughland, C., Catts, S. V., Mowry, B., Weickert, T. W., Shannon Weickert, C., Carr, V., Lenroot, R., Pantelis, C., & Zalesky, A. (2017). White Matter Disruptions in Schizophrenia Are Spatially Widespread and Topologically Converge on Brain Network Hubs. *Schizophrenia Bulletin*, *43*(2), 425–435. https://doi.org/10.1093/schbul/sbw100

Koshiyama, D., Kirihara, K., Tada, M., Nagai, T., Fujioka, M., Usui, K., Araki, T., & Kasai, K. (2020). Reduced Auditory Mismatch Negativity Reflects Impaired Deviance Detection in Schizophrenia. *Schizophrenia Bulletin*, *46*(4), 937–946.

https://doi.org/10.1093/schbul/sbaa006

Kostova, M., Passerieux, C., Laurent, J.-P., & Hardy-Baylé, M.-C. (2005). N400 anomalies in schizophrenia are correlated with the severity of formal thought disorder. *Schizophrenia Research*, *78*(2–3), 285–291. https://doi.org/10.1016/j.schres.2005.05.015

Kuperberg, G. R., Deckersbach, T., Holt, D. J., Goff, D., & West, W. C. (2007). Increased Temporal and Prefrontal Activity in Response to Semantic Associations in Schizophrenia. *Archives of General Psychiatry*, *64*(2), 138–151. https://doi.org/10.1001/archpsyc.64.2.138

Kuperberg, G. R., Delaney-Busch, N., Fanucci, K., & Blackford, T. (2018). Priming production: Neural evidence for enhanced automatic semantic activity preceding language production in schizophrenia. *NeuroImage. Clinical*, *18*, 74–85. https://doi.org/10.1016/j.nicl.2017.12.026

Kurata, K., & Tanji, J. (1986). Premotor cortex neurons in macaques: Activity before distal and proximal forelimb movements. *Journal of Neuroscience*, *6*(2), 403–411. https://doi.org/10.1523/JNEUROSCI.06-02-00403.1986

Kutas, M., & Federmeier, K. D. (2011). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology*, *62*, 621–647. https://doi.org/10.1146/annurev.psych.093008.131123

Kwapil, T. R., & Barrantes-Vidal, N. (2015). Schizotypy: Looking Back and Moving Forward. *Schizophrenia Bulletin*, *41*(Suppl 2), S366–S373. https://doi.org/10.1093/schbul/sbu186

La Corte, E., Eldahaby, D., Greco, E., Aquino, D., Bertolini, G., Levi, V., Ottenhausen, M., Demichelis, G., Romito, L. M., Acerbi, F., Broggi, M., Schiariti, M. P., Ferroli, P., Bruzzone, M. G., & Serrao, G. (2021). The Frontal Aslant Tract: A Systematic Review for Neurosurgical Applications. *Frontiers in Neurology*, *12*, 51. https://doi.org/10.3389/fneur.2021.641586

Lakoff, G., & Johnson, M. (2008). *Metaphors We Live By. 1980*. University of Chicago Press.

Langdon, R., Coltheart, M., Ward, P. B., & Catts, S. V. (2002). Disturbed communication in schizophrenia: The role of poor pragmatics and poor mind-reading. *Psychological Medicine*, *32*(7), 1273–1284.

Lavelle, M., Healey, P. G. T., & McCabe, R. (2013). Is Nonverbal Communication Disrupted in Interactions Involving Patients With Schizophrenia? *Schizophrenia Bulletin*, *39*(5), 1150–1158. https://doi.org/10.1093/schbul/sbs091

Lehrl, S., Triebig, G., & Fischer, B. (1995). Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurologica Scandinavica*, *91*(5), 335–345. https://doi.org/10.1111/j.1600-0404.1995.tb07018.x

Lesage, E., Hansen, P. C., & Miall, R. C. (2017). Right Lateral Cerebellum Represents Linguistic Predictability. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *37*(26), 6231–6241. https://doi.org/10.1523/JNEUROSCI.3203-16.2017

Lesourd, M., Osiurak, F., Baumard, J., Bartolo, A., Vanbellingen, T., & Reynaud, E. (2018). Cerebral correlates of imitation of intransitive gestures: An integrative review of neuroimaging data and brain lesion studies. *Neuroscience and Biobehavioral Reviews*, *95*, 44–60. https://doi.org/10.1016/j.neubiorev.2018.07.019

Leucht, S., Samara, M., Heres, S., & Davis, J. M. (2016). Dose Equivalents for Antipsychotic Drugs: The DDD Method. *Schizophrenia Bulletin*, *42*(Suppl 1), S90–S94. https://doi.org/10.1093/schbul/sbv167

Liu, J., Li, S., Li, X., Li, W., Yang, Y., Guo, S., Lv, L., Xiao, X., Yao, Y.-G., Guan, F., Li, M., & Luo, X.-J. (2021). Genome-wide association study followed by trans-ancestry meta-analysis identify 17 new risk loci for schizophrenia. *BMC Medicine*, *19*(1), 177. https://doi.org/10.1186/s12916-021-02039-9

Liu, N. H., Daumit, G. L., Dua, T., Aquila, R., Charlson, F., Cuijpers, P., Druss, B., Dudek, K., Freeman, M., Fujii, C., Gaebel, W., Hegerl, U., Levav, I., Munk Laursen, T., Ma, H., Maj, M., Elena Medina-Mora, M., Nordentoft, M., Prabhakaran, D., … Saxena, S. (2017). Excess mortality in persons with severe mental disorders: A multilevel intervention framework and priorities for clinical practice, policy and research agendas. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *16*(1), 30–40. https://doi.org/10.1002/wps.20384

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–157. https://doi.org/10.1038/35084005

Lotze, M., Heymans, U., Birbaumer, N., Veit, R., Erb, M., Flor, H., & Halsband, U. (2006). Differential cerebral activation during observation of expressive gestures and motor acts. *Neuropsychologia*, *44*(10), 1787–1795. https://doi.org/10.1016/j.neuropsychologia.2006.03.016

Lu, P.-Y., Huang, Y.-L., Huang, P.-C., Liu, Y.-C., Wei, S.-Y., Hsu, W.-Y., Chen, K. C., Chen, P. S., Wu, W.-C., Yang, Y. K., & Tseng, H.-H. (2021). Association of visual motor processing and social cognition in schizophrenia. *NPJ Schizophrenia*, *7*(1), 21. https://doi.org/10.1038/s41537-021-00150-7

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: A systematic review. *Archives of General Psychiatry*, *62*(9), 975–983. https://doi.org/10.1001/archpsyc.62.9.975

Martin, L. A. L., Koch, S. C., Hirjak, D., & Fuchs, T. (2016). Overcoming Disembodiment: The Effect of Movement Therapy on Negative Symptoms in Schizophrenia—A Multicenter Randomized Controlled Trial. *Frontiers in Psychology*, *7*. https://doi.org/10.3389/fpsyg.2016.00483

Martin, P., Tewesmeier, M., Albers, M., Schmid, G., & Scharfetter, C. (1994). Investigation of gestural and pantomime performance in chronic schizophrenic inpatients. *European Archives of Psychiatry and Clinical Neuroscience*, *244*(2), 59–64. https://doi.org/10.1007/BF02193520

Mashal, N., Vishne, T., & Laor, N. (2014). The role of the precuneus in metaphor comprehension: Evidence from an fMRI study in people with schizophrenia and healthy participants. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00818

Mashal, N., Vishne, T., Laor, N., & Titone, D. (2013). Enhanced left frontal involvement during novel metaphor comprehension in schizophrenia: Evidence from functional neuroimaging. *Brain and Language*, *124*(1), 66–74. https://doi.org/10.1016/j.bandl.2012.11.012

Mathalon, D. H., Faustman, W. O., & Ford, J. M. (2002). N400 and automatic semantic processing abnormalities in patients with schizophrenia. *Archives of General Psychiatry*, *59*(7), 641–648. https://doi.org/10.1001/archpsyc.59.7.641

Matthews, N., Gold, B. J., Sekuler, R., & Park, S. (2013). Gesture Imitation in Schizophrenia. *Schizophrenia Bulletin*, *39*(1), 94–101. https://doi.org/10.1093/schbul/sbr062

McDonald, B., Highley, J. R., Walker, M. A., Herron, B. M., Cooper, S. J., Esiri, M. M., & Crow, T. J. (2000). Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: A postmortem study. *The American Journal of Psychiatry*, *157*(1), 40–47. https://doi.org/10.1176/ajp.157.1.40

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, *30*, 67–76. https://doi.org/10.1093/epirev/mxn001

McNeill, D. (1992). *Hand and Mind: What Gestures Reveal about Thought* (Zentralbibliothek). University of Chicago Press.

Mehta, U. M., Thirthalli, J., Aneelraj, D., Jadhav, P., Gangadhar, B. N., & Keshavan, M. S. (2014). Mirror neuron dysfunction in schizophrenia and its functional implications: A systematic review. *Schizophrenia Research*, *160*(1–3), 9–19. https://doi.org/10.1016/j.schres.2014.10.040

Miller, E. (1984). Verbal fluency as a function of a measure of verbal intelligence and in relation to different types of cerebral pathology. *British Journal of Clinical Psychology*, *23*(1), 53–57. https://doi.org/10.1111/j.2044-8260.1984.tb00626.x

Millman, Z. B., Goss, J., Schiffman, J., Mejias, J., Gupta, T., & Mittal, V. A. (2014). Mismatch and Lexical Retrieval Gestures are Associated with Visual Information Processing, Verbal Production, and Symptomatology in Youth at High Risk for Psychosis. *Schizophrenia Research*, *158*(0), 64–68. https://doi.org/10.1016/j.schres.2014.06.007

Minzenberg, M. J., Ober, B. A., & Vinogradov, S. (2002). Semantic priming in schizophrenia: A review and synthesis. *Journal of the International Neuropsychological Society: JINS*, *8*(5), 699–720. https://doi.org/10.1017/s1355617702801357

Mitchell, R. L. C., & Crow, T. J. (2005). Right hemisphere language functions and schizophrenia: The forgotten hemisphere? *Brain*, *128*(5), 963–978. https://doi.org/10.1093/brain/awh466

Mitra, S., Mahintamani, T., Kavoor, A. R., & Nizamie, S. H. (2016). Negative symptoms in schizophrenia. *Industrial Psychiatry Journal*, *25*(2), 135–144. https://doi.org/10.4103/ipj.ipj_30_15

Mizuno, Y., Wartelsteiner, F., & Frajo-Apor, B. (2016). Resilience research in schizophrenia: A review of recent developments. *Current Opinion in Psychiatry*, *29*(3), 218–223. https://doi.org/10.1097/YCO.0000000000000248

Mohammad, O. M., & DeLisi, L. E. (2013). N400 in schizophrenia patients. *Current Opinion in Psychiatry*, *26*(2), 196–207. https://doi.org/10.1097/YCO.0b013e32835d9e56

Mossaheb, N., Aschauer, H. N., Stoettner, S., Schmoeger, M., Pils, N., Raab, M., & Willinger, U. (2014). Comprehension of metaphors in patients with schizophrenia-spectrum disorders. *Comprehensive Psychiatry*, *55*(4), 928–937. https://doi.org/10.1016/j.comppsych.2013.12.021

Murru, A., & Carpiniello, B. (2018). Duration of untreated illness as a key to early intervention in schizophrenia: A review. *Neuroscience Letters*, *669*, 59–67. https://doi.org/10.1016/j.neulet.2016.10.003

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews. Neuroscience*, *9*(11), 856–869. https://doi.org/10.1038/nrn2478

Nagels, A., Chatterjee, A., Kircher, T., & Straube, B. (2013). The role of semantic abstractness and perceptual category in processing speech accompanied by gestures. *Frontiers in Behavioral Neuroscience*, *7*. https://doi.org/10.3389/fnbeh.2013.00181

Nagels, A., Kauschke, C., Schrauf, J., Whitney, C., Straube, B., & Kircher, T. (2013). Neural substrates of figurative language during natural speech perception: An fMRI study. *Frontiers in Behavioral Neuroscience*, *7*. https://doi.org/10.3389/fnbeh.2013.00121

Nagels, A., Kircher, T., Grosvald, M., Steines, M., & Straube, B. (2019). Evidence for gesture-speech mismatch detection impairments in schizophrenia. *Psychiatry Research*, *273*, 15–21. https://doi.org/10.1016/j.psychres.2018.12.107

Nagels, A., Kircher, T., Steines, M., Grosvald, M., & Straube, B. (2015). A brief self-rating scale for the assessment of individual differences in gesture perception and production. *Learning and Individual Differences*. https://doi.org/10.1016/j.lindif.2015.03.008

Nagels, A., Kircher, T., Steines, M., & Straube, B. (2015). Feeling addressed! The role of body orientation and co-speech gesture in social communication. *Human Brain Mapping*, *36*(5), 1925–1936. https://doi.org/10.1002/hbm.22746

Nath, M., Wong, T. P., & Srivastava, L. K. (2021). Neurodevelopmental insights into circuit dysconnectivity in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *104*, 110047. https://doi.org/10.1016/j.pnpbp.2020.110047

Neely, J. H. (1991). Semantic priming effects in visual word recognition: A selective review of current findings and theories. In *Basic processes in reading: Visual word recognition* (pp. 264–336). Lawrence Erlbaum Associates, Inc.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(24), 9868–9872. https://doi.org/10.1073/pnas.87.24.9868

Olabi, B., Ellison-Wright, I., McIntosh, A. M., Wood, S. J., Bullmore, E., & Lawrie, S. M. (2011). Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biological Psychiatry*, *70*(1), 88–96. https://doi.org/10.1016/j.biopsych.2011.01.032

Özçalışkan, Ş., & Dimitrova, N. (2013). How Gesture Input Provides a Helping Hand to Language Development. *Seminars in Speech and Language*, *34*(4), 227–236. https://doi.org/10.1055/s-0033-1353447

Özçalışkan, Ş., & Goldin-Meadow, S. (2005). Gesture is at the cutting edge of early language development. *Cognition*, *96*(3), B101–B113. https://doi.org/10.1016/j.cognition.2005.01.001

Özyürek, A. (2014). Hearing and seeing meaning in speech and gesture: Insights from brain and behaviour. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1651), 20130296. https://doi.org/10.1098/rstb.2013.0296

Özyürek, A., Willems, R. M., Kita, S., & Hagoort, P. (2007). On-line Integration of Semantic Information from Speech and Gesture: Insights from Event-related Brain Potentials. *Journal of Cognitive Neuroscience*, *19*(4), 605–616. https://doi.org/10.1162/jocn.2007.19.4.605

Palmer, B. W., Martin, A. S., Depp, C. A., Glorioso, D. K., & Jeste, D. V. (2014). Wellness within illness: Happiness in schizophrenia. *Schizophrenia Research*, *159*(1), 151–156. https://doi.org/10.1016/j.schres.2014.07.027

Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S. E., Bishop, S., Cameron, D., Hamshere, M. L., Han, J., Hubbard, L., Lynham, A., Mantripragada, K., Rees, E., MacCabe, J. H., McCarroll, S. A., Baune, B. T., Breen, G., … Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics*, *50*(3), 381–389. https://doi.org/10.1038/s41588-018-0059-2

Park, S., Matthews, N., & Gibson, C. (2008). Imitation, Simulation, and Schizophrenia. *Schizophrenia Bulletin*, *34*(4), 698–707. https://doi.org/10.1093/schbul/sbn048

Parola, A., Berardinelli, L., & Bosco, F. M. (2018). Cognitive abilities and theory of mind in explaining communicative-pragmatic disorders in patients with schizophrenia. *Psychiatry Research*, *260*, 144–151. https://doi.org/10.1016/j.psychres.2017.11.051

Parola, A., Salvini, R., Gabbatore, I., Colle, L., Berardinelli, L., & Bosco, F. M. (2020). Pragmatics, Theory of Mind and executive functions in schizophrenia: Disentangling the puzzle using machine learning. *PLoS ONE*, *15*(3). https://doi.org/10.1371/journal.pone.0229603

Patel, G. H., Arkin, S. C., Ruiz-Betancourt, D. R., DeBaun, H. M., Strauss, N. E., Bartel, L. P., Grinband, J., Martinez, A., Berman, R. A., Leopold, D. A., & Javitt, D. C. (2020). What you see is what you get: Visual scanning failures of naturalistic social scenes in schizophrenia. *Psychological Medicine*, 1–10. https://doi.org/10.1017/S0033291720001646

Pauling, L. (1935). The Oxygen Equilibrium of Hemoglobin and Its Structural Interpretation. *Proceedings of the National Academy of Sciences of the United States of America*, *21*(4), 186–191. https://doi.org/10.1073/pnas.21.4.186

Pekkola, J., Laasonen, M., Ojanen, V., Autti, T., Jääskeläinen, I. P., Kujala, T., & Sams, M. (2006). Perception of matching and conflicting audiovisual speech in dyslexic and fluent readers: An fMRI study at 3 T. *NeuroImage*, *29*(3), 797–807. https://doi.org/10.1016/j.neuroimage.2005.09.069

Pooley, R. A. (2005). Fundamental Physics of MR Imaging. *RadioGraphics*, *25*(4), 1087–1099. https://doi.org/10.1148/rg.254055027

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Power, J. D., Schlaggar, B. L., & Petersen, S. E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *NeuroImage*, *105*, 536–551. https://doi.org/10.1016/j.neuroimage.2014.10.044

Prabhakar, G. (2016, May 27). *Flip angle | Radiology Reference Article | Radiopaedia.org*. Radiopaedia. https://radiopaedia.org/articles/flip-angle

Preston, D. C. (2016, April 7). *MRI  Basics*. Magnetic Resonance Imaging (MRI) of the Brain and Spine: Basics. https://case.edu/med/neurology/NR/MRI%20Basics.htm

Proverbio, A. M., Gabaro, V., Orlandi, A., & Zani, A. (2015). Semantic brain areas are involved in gesture comprehension: An electrical neuroimaging study. *Brain and Language*, *147*, 30–40. https://doi.org/10.1016/j.bandl.2015.05.002

Rapp, A. M., Langohr, K., Mutschler, D. E., Klingberg, S., Wild, B., & Erb, M. (2013). Isn't it ironic? Neural Correlates of Irony Comprehension in Schizophrenia. *PLoS ONE*, *8*(9). https://doi.org/10.1371/journal.pone.0074224

Ray, J. J. (1983). Reviving the Problem of Acquiescent Response Bias. *The Journal of Social Psychology*, *121*(1), 81–96. https://doi.org/10.1080/00224545.1983.9924470

Riedl, L., Nagels, A., Sammer, G., Choudhury, M., Nonnenmann, A., Sütterlin, A., Feise, C., Haslach, M., Bitsch, F., & Straube, B. (2021). *Multimodal Speech-Gesture Training in Patients With Schizophrenia Spectrum Disorder: Effects on Quality of Life and Neural Processing*. PsyArXiv. https://doi.org/10.31234/osf.io/a8wn4

Riedl, L., Nagels, A., Sammer, G., & Straube, B. (2020). A multimodal speech-gesture training intervention for patients with schizophrenia and its neural underpinnings – the study protocol of a randomized controlled pilot trial. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00110

Rilling, J., Glasser, M. F., Jbabdi, S., Andersson, J., & Preuss, T. M. (2012). Continuity, Divergence, and the Evolution of Brain Language Pathways. *Frontiers in Evolutionary Neuroscience*, *3*. https://doi.org/10.3389/fnevo.2011.00011

Rinck, P. A. (2022). *Magnetic Resonance in Medicine – The Textbook – Free Offprints | The Round Table Foundation TRTF – European Magnetic Resonance Forum EMRF.* http://trtf.eu/textbook.htm

Rizzolatti, G. (2005). The mirror neuron system and its function in humans. *Anatomy and Embryology*, *210*(5–6), 419–421. https://doi.org/10.1007/s00429-005-0039-z

Rizzolatti, G., & Arbib, M. A. (1998). Language within our grasp. *Trends in Neurosciences*, *21*(5), 188–194. https://doi.org/10.1016/S0166-2236(98)01260-0

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Brain Research. Cognitive Brain Research*, *3*(2), 131–141.

Rolls, E. T., Joliot, M., & Tzourio-Mazoyer, N. (2015). Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. *NeuroImage*, *122*, 1–5. https://doi.org/10.1016/j.neuroimage.2015.07.075

Rossetti, I., Brambilla, P., & Papagno, C. (2018). Metaphor Comprehension in Schizophrenic Patients. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.00670

Runge, V. M. (2018). *The Physics of Clinical MR Taught Through Images*. Thieme Medical Publishers, Incorporated. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/ulbmuenster/detail.action?docID=5379858.

Salisbury, D. (2010). N400 to lexical ambiguity and semantic incongruity in schizophrenia. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *75*(2), 127–132. https://doi.org/10.1016/j.ijpsycho.2009.10.002

Sammet, S. (2016). Magnetic Resonance Safety. *Abdominal Radiology (New York)*, *41*(3), 444–451. https://doi.org/10.1007/s00261-016-0680-4

Schettino, A., Lauro, L. R., Crippa, F., Anselmetti, S., Cavallaro, R., & Papagno, C. (2010). The comprehension of idiomatic expressions in schizophrenic patients. *Neuropsychologia*, *48*(4), 1032–1040. https://doi.org/10.1016/j.neuropsychologia.2009.11.030

Schneider, S., Wagels, L., Haeussinger, F. B., Fallgatter, A. J., Ehlis, A.-C., & Rapp, A. M. (2015). Haemodynamic and electrophysiological markers of pragmatic language comprehension in schizophrenia. *The World Journal of Biological Psychiatry*, *16*(6), 398–410. https://doi.org/10.3109/15622975.2015.1019359

Schülke, R., & Straube, B. (2017). Modulating the assessment of semantic speech–gesture relatedness via transcranial direct current stimulation of the left frontal cortex. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *10*(2), 223–230. https://doi.org/10.1016/j.brs.2016.10.012

Schülke, R., & Straube, B. (2019). Transcranial Direct Current Stimulation Improves Semantic Speech–Gesture Matching in Patients With Schizophrenia Spectrum Disorder. *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sby144

Seeman, P. (2009). Glutamate and dopamine components in schizophrenia. *Journal of Psychiatry & Neuroscience: JPN*, *34*(2), 143–149.

Sela, T., Lavidor, M., & Mitchell, R. L. C. (2015). A possible contributory mechanism for impaired idiom perception in schizophrenia. *Psychiatry Research*, *229*(1), 1–11. https://doi.org/10.1016/j.psychres.2015.07.021

Sharpe, V., Weber, K., & Kuperberg, G. R. (2020). Impairments in Probabilistic Prediction and Bayesian Learning Can Explain Reduced Neural Semantic Priming in Schizophrenia. *Schizophrenia Bulletin*, *46*(6), 1558–1566. https://doi.org/10.1093/schbul/sbaa069

Shenhav, A., Botvinick, M. M., & Cohen, J. D. (2013). The Expected Value of Control: An Integrative Theory of Anterior Cingulate Cortex Function. *Neuron*, *79*(2), 217–240. https://doi.org/10.1016/j.neuron.2013.07.007

Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research*, *49*(1–2), 1–52. https://doi.org/10.1016/s0920-9964(01)00163-3

Siddi, S., Petretto, D. R., Scanu, R., Burrai, C., Baita, A., Trincas, P., Trogu, E., Campus, L., Contu, A., & Preti, A. (2016). Deficits in metaphor but not in idiomatic processing are related to verbal hallucinations in patients with psychosis. *Psychiatry Research*, *246*, 101–112. https://doi.org/10.1016/j.psychres.2016.09.024

Skipper-Kallal, L. M., Mirman, D., & Olson, I. R. (2015). Converging evidence from fMRI and aphasia that the left temporoparietal cortex has an essential role in representing abstract semantic knowledge. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *69*, 104–120. https://doi.org/10.1016/j.cortex.2015.04.021

Slotnick, S. D. (2017). Cluster success: FMRI inferences for spatial extent have acceptable false-positive rates. *Cognitive Neuroscience*, *8*(3), 150–155. https://doi.org/10.1080/17588928.2017.1319350

Slotnick, S. D., Moo, L. R., Segal, J. B., & Hart, J. (2003). Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. *Cognitive Brain Research*, *17*(1), 75–82. https://doi.org/10.1016/S0926-6410(03)00082-X

Soares, J. M., Magalhães, R., Moreira, P. S., Sousa, A., Ganz, E., Sampaio, A., Alves, V., Marques, P., & Sousa, N. (2016). A Hitchhiker's Guide to Functional Magnetic Resonance Imaging. *Frontiers in Neuroscience*, *10*. https://doi.org/10.3389/fnins.2016.00515

Sommer, I., Ramsey, N., Kahn, R., Aleman, A., & Bouma, A. (2001). Handedness, language lateralisation and anatomical asymmetry in schizophrenia: Meta-analysis. *The British Journal of Psychiatry: The Journal of Mental Science*, *178*, 344–351. https://doi.org/10.1192/bjp.178.4.344

Spitzer, M., Weisker, I., Winter, M., Maier, S., Hermle, L., & Maher, B. A. (1994). Semantic and phonological priming in schizophrenia. *Journal of Abnormal Psychology*, *103*(3), 485. https://doi.org/10.1037/0021-843X.103.3.485

Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers*, *31*(1), 137–149. https://doi.org/10.3758/BF03207704

Stegmayer, K., Bohlhalter, S., Vanbellingen, T., Federspiel, A., Moor, J., Wiest, R., Müri, R., Strik, W., & Walther, S. (2016). Structural brain correlates of defective gesture performance in schizophrenia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *78*, 125–137. https://doi.org/10.1016/j.cortex.2016.02.014

Stegmayer, K., Horn, H., Federspiel, A., Razavi, N., Bracht, T., Laimböck, K., Strik, W., Dierks, T., Wiest, R., Müller, T. J., & Walther, S. (2014). Supplementary motor area (SMA) volume is associated with psychotic aberrant motor behaviour of patients with schizophrenia. *Psychiatry Research: Neuroimaging*, *223*(1), 49–51. https://doi.org/10.1016/j.pscychresns.2014.05.002

Stegmayer, K., Moor, J., Vanbellingen, T., Bohlhalter, S., Müri, R. M., Strik, W., & Walther, S. (2016). Gesture Performance in First- and Multiple-Episode Patients with Schizophrenia Spectrum Disorders. *Neuropsychobiology*, *73*(4), 201–208. https://doi.org/10.1159/000446116

Steines, M., Nagels, A., Kircher, T., & Straube, B. (2021). The role of the left and right inferior frontal gyrus in processing metaphoric and unrelated co-speech gestures. *NeuroImage*, *237*, 118182. https://doi.org/10.1016/j.neuroimage.2021.118182

Straube, B., Green, A., Bromberger, B., & Kircher, T. (2011). The differentiation of iconic and metaphoric gestures: Common and unique integration processes. *Human Brain Mapping*, *32*(4), 520–533. https://doi.org/10.1002/hbm.21041

Straube, B., Green, A., Sass, K., & Kircher, T. (2014). Superior Temporal Sulcus Disconnectivity During Processing of Metaphoric Gestures in Schizophrenia. *Schizophrenia Bulletin*, *40*(4), 936–944. https://doi.org/10.1093/schbul/sbt110

Straube, B., Green, A., Sass, K., Kirner-Veselinovic, A., & Kircher, T. (2013). Neural integration of speech and gesture in schizophrenia: Evidence for differential processing of metaphoric gestures. *Human Brain Mapping*, *34*(7), 1696–1712. https://doi.org/10.1002/hbm.22015

Straube, B., Green, A., Weis, S., Chatterjee, A., & Kircher, T. (2008). Memory Effects of Speech and Gesture Binding: Cortical and Hippocampal Activation in Relation to Subsequent Memory Performance. *Journal of Cognitive Neuroscience*, *21*(4), 821–836. https://doi.org/10.1162/jocn.2009.21053

Straube, B., Green, A., Weis, S., Chatterjee, A., & TiloKircher. (2009). Memory Effects of Speech and Gesture Binding: Cortical and Hippocampal Activation in Relation to Subsequent Memory Performance. *Journal of Cognitive Neuroscience*, *21*(4), 821–836. https://doi.org/10.1162/jocn.2009.21053

Straube, B., Green, A., Weis, S., & Kircher, T. (2012). A Supramodal Neural Network for Speech and Gesture Semantics: An fMRI Study. *PLoS ONE*, *7*(11). https://doi.org/10.1371/journal.pone.0051207

Straube, B., He, Y., Steines, M., Gebhardt, H., Kircher, T., Sammer, G., & Nagels, A. (2013). Supramodal neural processing of abstract information conveyed by speech and gesture. *Frontiers in Behavioral Neuroscience*, *7*. https://doi.org/10.3389/fnbeh.2013.00120

Straube, B., Meyer, L., Green, A., & Kircher, T. (2014). Semantic relation vs. surprise: The differential effects of related and unrelated co-verbal gestures on neural encoding and subsequent recognition. *Brain Research*, *1567*, 42–56. https://doi.org/10.1016/j.brainres.2014.04.012

Straube, B., Wroblewski, A., Jansen, A., & He, Y. (2018). The connectivity signature of co-speech gesture integration: The superior temporal sulcus modulates connectivity between areas related to visual gesture and auditory speech processing. *NeuroImage*, *181*, 539–549. https://doi.org/10.1016/j.neuroimage.2018.07.037

Subramaniam, K., Luks, T. L., Garrett, C., Chung, C., Fisher, M., Nagarajan, S., & Vinogradov, S. (2014). Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. *NeuroImage*, *99*, 281–292. https://doi.org/10.1016/j.neuroimage.2014.05.057

Surguladze, S. A., Calvert, G. A., Brammer, M. J., Campbell, R., Bullmore, E. T., Giampietro, V., & David, A. S. (2001). Audio–visual speech perception in schizophrenia: An fMRI study. *Psychiatry Research: Neuroimaging*, *106*(1), 1–14. https://doi.org/10.1016/S0925-4927(00)00081-0

Szycik, G. R., Münte, T. F., Dillo, W., Mohammadi, B., Samii, A., Emrich, H. M., & Dietrich, D. E. (2009). Audiovisual integration of speech is disturbed in schizophrenia: An fMRI study. *Schizophrenia Research*, *110*(1), 111–118. https://doi.org/10.1016/j.schres.2009.03.003

Thakkar, K. N., Peterman, J. S., & Park, S. (2014). Altered Brain Activation During Action Imitation and Observation in Schizophrenia: A Translational Approach to Investigating Social Dysfunction in Schizophrenia. *The American Journal of*

*Psychiatry*, *171*(5), 539–548. https://doi.org/10.1176/appi.ajp.2013.13040498

Thoma, P., & Daum, I. (2006). Neurocognitive mechanisms of figurative language processing—Evidence from clinical dysfunctions. *Neuroscience & Biobehavioral Reviews*, *30*(8), 1182–1205. https://doi.org/10.1016/j.neubiorev.2006.09.001

Tremblay, P., & Gracco, V. L. (2009). Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS). *Brain Research*, *1268*, 112–124. https://doi.org/10.1016/j.brainres.2009.02.076

Troisi, A., Spalletta, G., & Pasini, A. (1998). Non-verbal behaviour deficits in schizophrenia: An ethological study of drug-free patients. *Acta Psychiatrica Scandinavica*, *97*(2), 109–115. https://doi.org/10.1111/j.1600-0447.1998.tb09971.x

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage*, *15*(1), 273–289. https://doi.org/10.1006/nimg.2001.0978

Varga, E., Schnell, Z., Tényi, T., Németh, N., Simon, M., Hajnal, A., Horváth, R. A., Hamvas, E., Járai, R., Fekete, S., & Herold, R. (2014). Compensatory effect of general cognitive skills on non-literal language processing in schizophrenia: A preliminary study. *Journal of Neurolinguistics*, *29*(1), 1–16. https://doi.org/10.1016/j.jneuroling.2014.01.001

Viher, P. V., Abdulkadir, A., Savadijev, P., Stegmayer, K., Kubicki, M., Makris, N., Karmacharya, S., Federspiel, A., Bohlhalter, S., Vanbellingen, T., Müri, R., Wiest, R., Strik, W., & Walther, S. (2020). Structural organization of the praxis network predicts gesture production: Evidence from healthy subjects and patients with schizophrenia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *132*, 322–333. https://doi.org/10.1016/j.cortex.2020.05.023

Viher, P. V., Stegmayer, K., Kubicki, M., Karmacharya, S., Lyall, A. E., Federspiel, A., Vanbellingen, T., Bohlhalter, S., Wiest, R., Strik, W., & Walther, S. (2018). The cortical signature of impaired gesturing: Findings from schizophrenia. *NeuroImage: Clinical*, *17*, 213–221. https://doi.org/10.1016/j.nicl.2017.10.017

Villarreal, M., Fridman, E. A., Amengual, A., Falasco, G., Gerscovich, E. R., Ulloa, E. R., & Leiguarda, R. C. (2008). The neural substrate of gesture recognition. *Neuropsychologia*, *46*(9), 2371–2382. https://doi.org/10.1016/j.neuropsychologia.2008.03.004

Vlcek, P., Bob, P., & Raboch, J. (2014). Sensory disturbances, inhibitory deficits, and the P50 wave in schizophrenia. *Neuropsychiatric Disease and Treatment*, *10*, 1309–1315. https://doi.org/10.2147/NDT.S64219

Vukovic, N., Feurra, M., Shpektor, A., Myachykov, A., & Shtyrov, Y. (2017). Primary motor cortex functionally contributes to language comprehension: An online rTMS study. *Neuropsychologia*, *96*, 222–229. https://doi.org/10.1016/j.neuropsychologia.2017.01.025

Walter, H. (2017). Research Domain Criteria (RDoC). *Der Nervenarzt*, *88*(5), 538–548. https://doi.org/10.1007/s00115-017-0284-4

Walther, S., Eisenhardt, S., Bohlhalter, S., Vanbellingen, T., Müri, R., Strik, W., & Stegmayer, K. (2016). Gesture Performance in Schizophrenia Predicts Functional Outcome After 6 Months. *Schizophrenia Bulletin*, *42*(6), 1326–1333. https://doi.org/10.1093/schbul/sbw124

Walther, S., Kunz, M., Müller, M., Zürcher, C., Vladimirova, I., Bachofner, H., Scherer, K. A., Nadesalingam, N., Stegmayer, K., Bohlhalter, S., & Viher, P. V. (2019). Single Session Transcranial Magnetic Stimulation Ameliorates Hand Gesture Deficits in Schizophrenia. *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sbz078

Walther, S., & Mittal, V. A. (2016). Why We Should Take a Closer Look at Gestures. *Schizophrenia Bulletin*, *42*(2), 259–261. https://doi.org/10.1093/schbul/sbv229

Walther, S., Mittal, V. A., Stegmayer, K., & Bohlhalter, S. (2020). Gesture deficits and apraxia in schizophrenia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *133*, 65–75. https://doi.org/10.1016/j.cortex.2020.09.017

Walther, S., Schäppi, L., Federspiel, A., Bohlhalter, S., Wiest, R., Strik, W., & Stegmayer, K. (2017). Resting-State Hyperperfusion of the Supplementary Motor Area in Catatonia. *Schizophrenia Bulletin*, *43*(5), 972–981. https://doi.org/10.1093/schbul/sbw140

Walther, S., Stegmayer, K., Sulzbacher, J., Vanbellingen, T., Müri, R., Strik, W., & Bohlhalter, S. (2015). Nonverbal social communication and gesture control in schizophrenia. *Schizophrenia Bulletin*, *41*(2), 338–345. https://doi.org/10.1093/schbul/sbu222

Walther, S., Vanbellingen, T., Müri, R., Strik, W., & Bohlhalter, S. (2013a). Impaired pantomime in schizophrenia: Association with frontal lobe function. *Cortex*, *49*(2), 520–527. https://doi.org/10.1016/j.cortex.2011.12.008

Walther, S., Vanbellingen, T., Müri, R., Strik, W., & Bohlhalter, S. (2013b). Impaired gesture performance in schizophrenia: Particular vulnerability of meaningless pantomimes. *Neuropsychologia*, *51*(13), 2674–2678. https://doi.org/10.1016/j.neuropsychologia.2013.08.017

Warrier, C., Wong, P., Penhune, V., Zatorre, R., Parrish, T., Abrams, D., & Kraus, N. (2009). Relating Structure to Function: Heschl's Gyrus and Acoustic Processing. *Journal of Neuroscience*, *29*(1), 61–69. https://doi.org/10.1523/JNEUROSCI.3489-08.2009

White, T. P., Borgan, F., Ralley, O., & Shergill, S. S. (2016). You looking at me?: Interpreting social cues in schizophrenia. *Psychological Medicine*, *46*(1), 149–160. https://doi.org/10.1017/S0033291715001622

Wilke, M. (2014). Isolated Assessment of Translation or Rotation Severely Underestimates the Effects of Subject Motion in fMRI Data. *PLOS ONE*, *9*(10), e106498. https://doi.org/10.1371/journal.pone.0106498

Willems, R. M., Özyürek, A., & Hagoort, P. (2007). When Language Meets Action: The Neural Integration of Gesture and Speech. *Cerebral Cortex*, *17*(10), 2322–2333. https://doi.org/10.1093/cercor/bhl141

Willems, R. M., Ozyürek, A., & Hagoort, P. (2009). Differential roles for left inferior frontal and superior temporal cortex in multimodal integration of action and language.

*NeuroImage*, *47*(4), 1992–2004. https://doi.org/10.1016/j.neuroimage.2009.05.066

Wroblewski, A., He, Y., & Straube, B. (2019). Dynamic Causal Modelling suggests impaired effective connectivity in patients with schizophrenia spectrum disorders during gesture-speech integration. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2019.12.005

Wüthrich, F., Pavlidou, A., Stegmayer, K., Eisenhardt, S., Moor, J., Schäppi, L., Vanbellingen, T., Bohlhalter, S., & Walther, S. (2020). Nonverbal communication remains untouched: No beneficial effect of symptomatic improvement on poor gesture performance in schizophrenia. *Schizophrenia Research*, *223*, 258–264. https://doi.org/10.1016/j.schres.2020.08.013

Wüthrich, F., Viher, P. V., Stegmayer, K., Federspiel, A., Bohlhalter, S., Vanbellingen, T., Wiest, R., & Walther, S. (2020). Dysbalanced Resting-State Functional Connectivity Within the Praxis Network Is Linked to Gesture Deficits in Schizophrenia. *Schizophrenia Bulletin*, *46*(4), 905–915. https://doi.org/10.1093/schbul/sbaa008

Xu, J., Gannon, P. J., Emmorey, K., Smith, J. F., & Braun, A. R. (2009). Symbolic gestures and spoken language are processed by a common neural system. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(49), 20664–20669. https://doi.org/10.1073/pnas.0909197106

Yamamoto, M., Kushima, I., Suzuki, R., Branko, A., Kawano, N., Inada, T., Iidaka, T., & Ozaki, N. (2018). Aberrant functional connectivity between the thalamus and visual cortex is related to attentional impairment in schizophrenia. *Psychiatry Research: Neuroimaging*, *278*, 35–41. https://doi.org/10.1016/j.pscychresns.2018.06.007

Yamasue, H., Yamada, H., Yumoto, M., Kamio, S., Kudo, N., Uetsuki, M., Abe, O., Fukuda, R., Aoki, S., Ohtomo, K., Iwanami, A., Kato, N., & Kasai, K. (2004). Abnormal association between reduced magnetic mismatch field to speech sounds and smaller left planum temporale volume in schizophrenia. *NeuroImage*, *22*(2), 720–727. https://doi.org/10.1016/j.neuroimage.2004.01.042

Yang, F. G., Edens, J., Simpson, C., & Krawczyk, D. C. (2009). Differences in task demands influence the hemispheric lateralization and neural correlates of metaphor. *Brain and Language*, *111*(2), 114–124. https://doi.org/10.1016/j.bandl.2009.08.006

Yang, J., Andric, M., & Mathew, M. M. (2015). The neural basis of hand gesture comprehension: A meta-analysis of functional magnetic resonance imaging studies. *Neuroscience & Biobehavioral Reviews*, *57*, 88–104. https://doi.org/10.1016/j.neubiorev.2015.08.006

Yeung, J., & Murphy, A. (2011, June 20). *Spatial resolution (MRI). Reference Article. Radiopaedia.org*. Radiopaedia. https://radiopaedia.org/articles/spatial-resolution-mri-2

Yeung, N. (2013, December 1). *Conflict Monitoring and Cognitive Control*. The Oxford Handbook of Cognitive Neuroscience. https://doi.org/10.1093/oxfordhb/9780199988709.013.0018

Zeev-Wolf, M., Faust, M., Levkovitz, Y., Harpaz, Y., & Goldstein, A. (2015). Magnetoencephalographic evidence of early right hemisphere overactivation during metaphor comprehension in schizophrenia. *Psychophysiology*, *52*(6), 770–781. https://doi.org/10.1111/psyp.12408

Zeev-Wolf, M., Goldstein, A., Levkovitz, Y., & Faust, M. (2014). Fine-coarse semantic processing in schizophrenia: A reversed pattern of hemispheric dominance. *Neuropsychologia*, *56*, 119–128. https://doi.org/10.1016/j.neuropsychologia.2014.01.008

# 8. Appendix

## 8.1. Supplementary results tables

Supplementary Table 1: Neuropsychological battery

Significant group differences were observed for d2 speed, d2 concentration performance and the alternating verbal fluency test (sum). This points to an inconsistent concentration deficit in SSD patients. Correlation analyses with task performance and neural activation (eigenvariates extracted from the significant clusters of the main analysis in the left MTG, left IFG, vermis, right MSFG, right SMA and right STG for each condition) were not significant after correction for multiple testing (Bonferroni-corrected significance level: p < 0.00032).

| Neuropsychology | n controls | m | SD | n patients | m | SD | *t*-value | *p*-value |
|---|---|---|---|---|---|---|---|---|
| Empathy questionnaire | 36 | 3.3 | 0.6 | 42 | 3.2 | 0.6 | 0.34 | 0.73 |
| Gesture questionnaire (Nagels, Kircher, Steines, Grosvald, et al., 2015) | 36 | 3.3 | 0.6 | 42 | 3.3 | 0.5 | 0.09 | 0.93 |
| Gesture production | 36 | 3.2 | 0.7 | 42 | 3.1 | 0.7 | 0.53 | 0.60 |
| Gesture perception | 36 | 3.4 | 0.7 | 42 | 3.5 | 0.5 | -0.48 | 0.63 |
| Proverb-metaphor-test (Barth & Küfferle, 2001), sum | 36 | 15.6 | 3.5 | 42 | 18.7 | 6.4 | -2.72 | 0.01 |
| Multiple-choice word test B (Lehrl et al., 1995) (correct items out of 37) | 36 | 30.9 | 3.4 | 42 | 27.7 | 7.5 | 2.39 | 0.02 |
| Digit span (Blackburn & Benton, 1957) forward | 35 | 8.5 | 1.9 | 41 | 7.8 | 1.8 | 1.60 | 0.11 |
| Digit span backwards | 35 | 7.0 | 2.2 | 41 | 5.8 | 1.6 | 2.68 | 0.01 |
| Digit span sum | 35 | 15.4 | 3.5 | 41 | 13.6 | 2.9 | 2.51 | 0.01 |
| Trail making test (Bowie & Harvey, 2006) A (sec) | 35 | 26.3 | 9.4 | 41 | 31.1 | 10.1 | -2.14 | 0.04 |
| Trail making test B (sec) | 35 | 55.4 | 20.6 | 40 | 69.2 | 21.9 | -2.80 | 0.01 |
| d2 (Bates & Lemay, 2004) TN (speed) | 35 | 472.4 | 85.8 | 41 | 384.4 | 108.2 | 3.88 | *<0.01 |
| d2 E1 (omission errors) | 35 | 23.9 | 24.9 | 41 | 21.7 | 21.1 | 0.40 | 0.69 |
| d2 E2 (commission errors) | 35 | 0.8 | 1.8 | 41 | 1.3 | 2.5 | -1.00 | 0.32 |
| d2 CP (concentration performance) | 35 | 179.7 | 43.9 | 41 | 142.0 | 40.3 | 3.90 | *<0.01 |
| Verbal fluency test(Miller, 1984), animals, sum | 31 | 23.9 | 6.4 | 41 | 19.6 | 5.9 | 2.99 | <0.01 |
| Verbal fluency test, animals, perseverations | 31 | 0.6 | 1.0 | 41 | 0.2 | 0.6 | 1.66 | 0.10 |
| Verbal fluency test, animals, errors | 31 | 0.5 | 1.2 | 41 | 0.2 | 0.5 | 1.33 | 0.19 |
| Verbal fluency test, P, sum | 31 | 12.6 | 4.1 | 41 | 10.3 | 4.3 | 2.27 | 0.03 |
| Verbal fluency test, P, perseverations | 31 | 0.2 | 0.6 | 41 | 0.3 | 0.9 | -0.49 | 0.62 |
| Verbal fluency test, P, errors | 31 | 0.8 | 1.1 | 41 | 0.4 | 0.7 | 1.87 | 0.07 |
| Verbal fluency test, alternating, sum | 31 | 15.8 | 2.6 | 41 | 12.0 | 3.6 | 4.90 | *<0.01 |
| Verbal fluency test, alternating, perseverations | 31 | 0.2 | 0.5 | 41 | 0.3 | 0.6 | -1.07 | 0.29 |
| Verbal fluency test, alternating, errors | 31 | 0.5 | 1.0 | 41 | 0.3 | 0.5 | 0.86 | 0.39 |

**Significance level < 0.0021 (Bonferroni-corrected)*

Supplementary Table 2: Effects of handedness

fMRI clusters resulting from the within-group contrast of abstract > concrete and unrelated > related speech-gesture pairs in patients, corrected at $p < 0.05$ (whole-brain analysis). For each cluster, MNI coordinates and t-values of the first peak voxel are listed. Anatomical regions refer to peak voxel localization based on the AAL toolbox (local maxima labeling) and cluster extent to the cluster labeling.

| *Group* | *Contrast* | *Hemisphere* | *Cluster extent* | *Anatomical region of peak* | *MNI coordinates* | | | *t-value* | *No. of voxels* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *x* | *y* | *z* | | |
| *All patients* | *abs > con* | *L + R* | *Left MTG, right STG, left STG* | *Left MTG* | -48 | -36 | -2 | *7.60* | *19116* |
| | | *L + R* | *Right calcarine sulcus, right LiG, left calcarine sulcus* | *Left PCC* | -2 | -40 | 24 | *4.81* | *12902* |
| *Right-handed patients* | *abs > con* | *L + R* | *Left MTG, left STG, right SFG, left SMA* | *Left MTG* | -50 | -36 | -2 | *7.98* | *135535* |
| | | *R* | *Right STG, right MTG, right insula* | *Right STG* | 56 | -8 | 0 | *6.35* | *8806* |
| | | *L + R* | *Right calcarine sulcus, right LiG* | *Left PCC* | -2 | -42 | 26 | *4.77* | *14250* |
| *All patients* | *unr > rel* | *L + R* | *Right MSFG, left MSFG, left SMA* | *Right MSFG* | 6 | 24 | 42 | *4.62* | *2487* |
| | | *R* | *Right IFG, right insula* | *Right IFG* | 48 | 42 | -12 | *4.37* | *1933* |
| | | *L* | *Left IFG, left insula* | *Left insula* | -28 | 18 | -8 | *4.05* | *1603* |
| *Right-handed patients* | *unr > rel* | *R* | *Right IFG, right insula* | *Right IFG* | 34 | 34 | -4 | *4.05* | *1695* |
| | | *L* | *Left IFG, left insula* | *Left insula* | -28 | 22 | -6 | *4.03* | *1322* |
| | | *R* | *Right MSFG, left MSFG, left SMA* | *Right MSFG* | 4 | 24 | 42 | *3.90* | *2179* |

*Abs, abstract condition; con, concrete condition; unr, unrelated condition; rel, related condition; L, left; R, right; MTG, middle temporal gyrus; STG, superior temporal gyrus; LiG, lingual gyrus; PCC, posterior cingulate cortex; SMA, supplementary motor area; MSFG, medial segment of superior frontal gyrus.*

Supplementary Table 3: Effects of sex on result clusters

Results of univariate ANOVAs. Dependent variables: eigenvariates extracted from the significant clusters of our contrasts of interest using the cluster function in SPM12. Factors: group, sex, abstractness, relatedness. Bonferroni-correction was applied for multiple comparisons.

| | Left MTG | | Left IFG | | Vermis | | Right MSFG | | Right SMA | | Right STG | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F | Sig. | F | Sig. | F | Sig. | F | Sig. | F | Sig. | F | Sig. |
| Group*sex | 0.30 | 0.58 | 2.43 | 0.12 | 1.12 | 0.29 | 0.19 | 0.67 | 0.06 | 0.80 | 6.60 | 0.01 |
| Group * sex * abstractness | 1.05 | 0.31 | 0.05 | 0.83 | 3.85 | 0.05 | 0.05 | 0.82 | 0.04 | 0.84 | 0.26 | 0.61 |
| Group * sex * relatedness | 0.24 | 0.62 | 0.37 | 0.54 | 0.22 | 0.64 | 0.10 | 0.75 | 4.70 | 0.03 | 0.29 | 0.59 |
| Group * sex * abstractness * relatedness | 3.96 | 0.05 | 2.07 | 0.15 | 0.79 | 0.38 | 0.83 | 0.36 | 0.07 | 0.79 | 2.55 | 0.11 |

Significance level $p < 0.0083$ (Bonferroni-corrected)

Supplementary Table 4: Effects of age

Pearson Correlations of age with the eigenvariates extracted from the significant clusters of our contrasts of interest in the main analysis using the cluster function in SPM12. Bonferroni-correction was applied for multiple comparisons. No significant correlations between age and neural data were found.

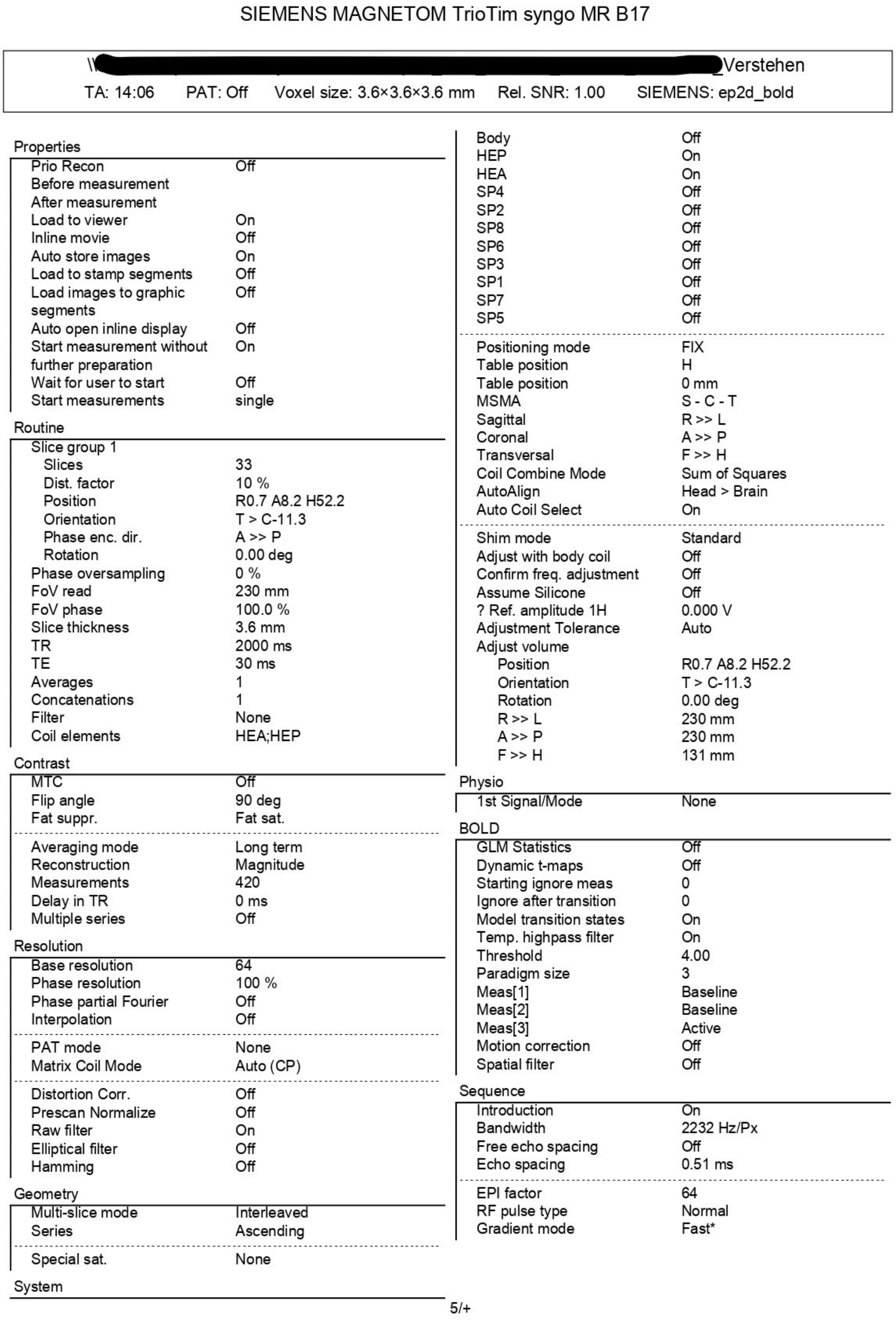
| | | *Conditions* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *AR* | | *AU* | | *CR* | | *CU* | |
| *Regions of interest* | | *Patients* | *Controls* | *Patients* | *Controls* | *Patients* | *Controls* | *Patients* | *Controls* |
| *Left MTG* | *Pearson Correlation* | *-0.116* | *0.336* | *-0.171* | *0.340* | *.014* | *.019* | *0.005* | *-0.007* |
| | *p-value (two-way)* | *0.463* | *0.045* | *0.278* | *0.043* | *.929* | *.912* | *0.974* | *0.966* |
| *Left IFG* | *Pearson Correlation* | *0.020* | *0.080* | *-0.035* | *0.194* | *.103* | *-0.267* | *0.076* | *0.094* |
| | *p-value (two-way)* | *0.900* | *0.643* | *0.828* | *0.256* | *.516* | *0.115* | *0.631* | *0.585* |
| *Vermis* | *Pearson Correlation* | *-0.059* | *0.020* | *0.204* | *0.104* | *.275* | *-0.239* | *-0.070* | *0.113* |
| | *p-value (two-way)* | *0.711* | *0.906* | *0.194* | *0.546* | *.078* | *0.160* | *0.658* | *0.511* |
| *Right MSFG* | *Pearson Correlation* | *0.243* | *0.218* | *0.083* | *0.365* | *-.090* | *-0.216* | *0.138* | *0.087* |
| | *p-value (two-way)* | *0.121* | *0.201* | *0.602* | *0.029* | *.570* | *0.205* | *0.384* | *0.613* |
| *Right SMA* | *Pearson Correlation* | *0.351* | *-0.122* | *-0.151* | *0.343* | *.201* | *-0.087* | *0.240* | *-0.098* |
| | *p-value (two-way)* | *0.023* | *0.480* | *0.338* | *0.041* | *.202* | *0.615* | *0.126* | *0.571* |
| *Right STG* | *Pearson Correlation* | *-0.072* | *-0.048* | *-0.057* | *0.044* | *-.158* | *-0.089* | *0.035* | *-0.042* |
| | *p-value (two-way)* | *0.651* | *0.782* | *0.722* | *0.799* | *.318* | *0.604* | *0.828* | *0.807* |

*Significance level $p < 0.001$ (Bonferroni-corrected)*

# 8.2. Study material

## 8.2.1. MRI properties

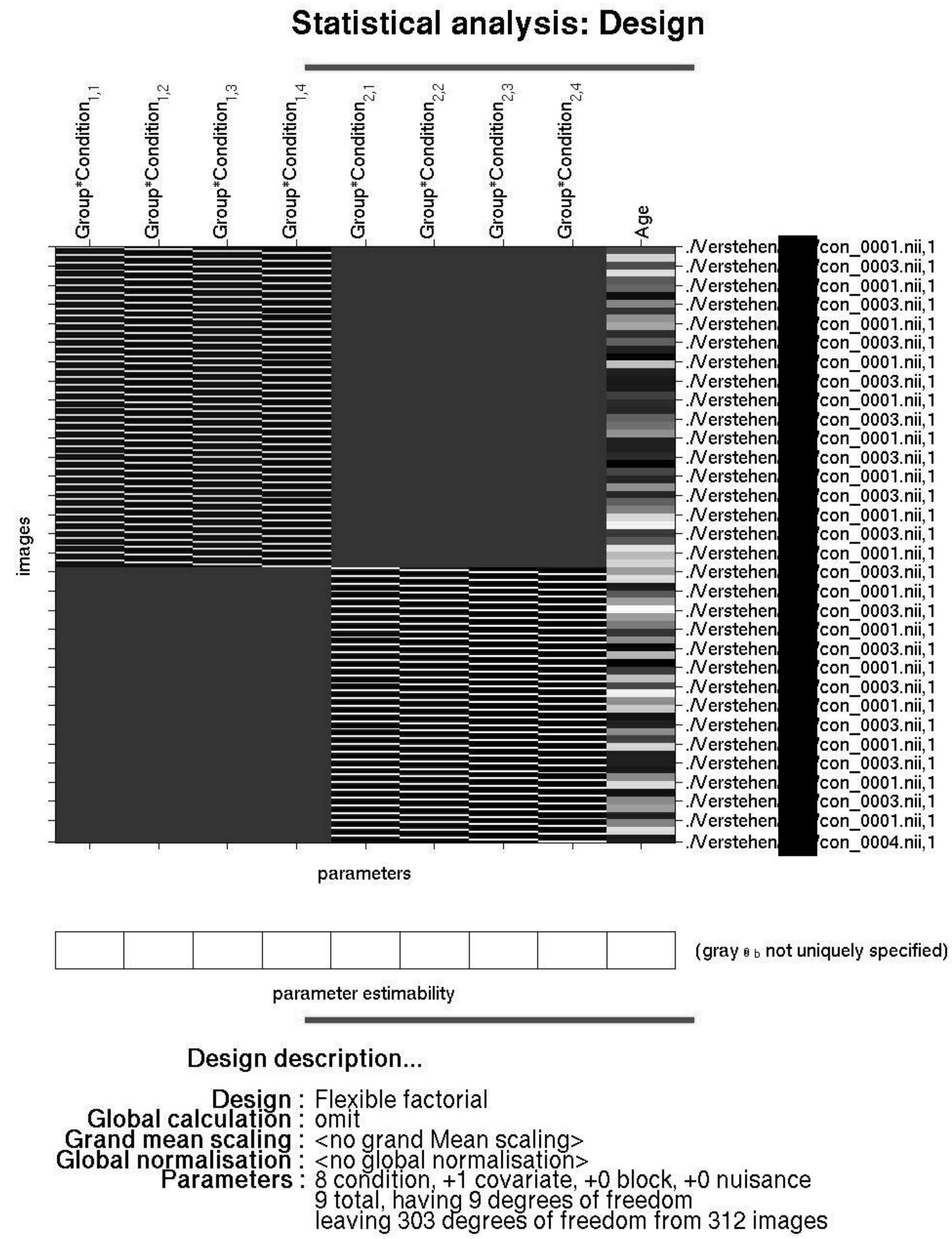
Supplementary Figure 1: MRI properties



```
SIEMENS MAGNETOM TrioTim syngo MR B17

\[redacted]_Verstehen
TA: 14:06   PAT: Off   Voxel size: 3.6×3.6×3.6 mm   Rel. SNR: 1.00   SIEMENS: ep2d_bold

Properties
  Prio Recon                          Off
  Before measurement
  After measurement
  Load to viewer                      On
  Inline movie                        Off
  Auto store images                   On
  Load to stamp segments              Off
  Load images to graphic              Off
  segments
  Auto open inline display            Off
  Start measurement without           On
  further preparation
  Wait for user to start              Off
  Start measurements                  single

Routine
  Slice group 1
    Slices                            33
    Dist. factor                      10 %
    Position                          R0.7 A8.2 H52.2
    Orientation                       T > C-11.3
    Phase enc. dir.                   A >> P
    Rotation                          0.00 deg
  Phase oversampling                  0 %
  FoV read                            230 mm
  FoV phase                           100.0 %
  Slice thickness                     3.6 mm
  TR                                  2000 ms
  TE                                  30 ms
  Averages                            1
  Concatenations                      1
  Filter                              None
  Coil elements                       HEA;HEP

Contrast
  MTC                                 Off
  Flip angle                          90 deg
  Fat suppr.                          Fat sat.
  - - - - - - - - - - - - - - - - - - - - - - -
  Averaging mode                      Long term
  Reconstruction                      Magnitude
  Measurements                        420
  Delay in TR                         0 ms
  Multiple series                     Off

Resolution
  Base resolution                     64
  Phase resolution                    100 %
  Phase partial Fourier               Off
  Interpolation                       Off
  - - - - - - - - - - - - - - - - - - - - - - -
  PAT mode                            None
  Matrix Coil Mode                    Auto (CP)
  - - - - - - - - - - - - - - - - - - - - - - -
  Distortion Corr.                    Off
  Prescan Normalize                   Off
  Raw filter                          On
  Elliptical filter                   Off
  Hamming                             Off

Geometry
  Multi-slice mode                    Interleaved
  Series                              Ascending
  - - - - - - - - - - - - - - - - - - - - - - -
  Special sat.                        None

System
  Body                                Off
  HEP                                 On
  HEA                                 On
  SP4                                 Off
  SP2                                 Off
  SP8                                 Off
  SP6                                 Off
  SP3                                 Off
  SP1                                 Off
  SP7                                 Off
  SP5                                 Off
  - - - - - - - - - - - - - - - - - - - - - - -
  Positioning mode                    FIX
  Table position                      H
  Table position                      0 mm
  MSMA                                S - C - T
  Sagittal                            R >> L
  Coronal                             A >> P
  Transversal                         F >> H
  Coil Combine Mode                   Sum of Squares
  AutoAlign                           Head > Brain
  Auto Coil Select                    On
  - - - - - - - - - - - - - - - - - - - - - - -
  Shim mode                           Standard
  Adjust with body coil               Off
  Confirm freq. adjustment            Off
  Assume Silicone                     Off
  ? Ref. amplitude 1H                 0.000 V
  Adjustment Tolerance                Auto
  Adjust volume
    Position                          R0.7 A8.2 H52.2
    Orientation                       T > C-11.3
    Rotation                          0.00 deg
    R >> L                            230 mm
    A >> P                            230 mm
    F >> H                            131 mm

Physio
  1st Signal/Mode                     None

BOLD
  GLM Statistics                      Off
  Dynamic t-maps                      Off
  Starting ignore meas                0
  Ignore after transition             0
  Model transition states             On
  Temp. highpass filter               On
  Threshold                           4.00
  Paradigm size                       3
  Meas[1]                             Baseline
  Meas[2]                             Baseline
  Meas[3]                             Active
  Motion correction                   Off
  Spatial filter                      Off

Sequence
  Introduction                        On
  Bandwidth                           2232 Hz/Px
  Free echo spacing                   Off
  Echo spacing                        0.51 ms
  - - - - - - - - - - - - - - - - - - - - - - -
  EPI factor                          64
  RF pulse type                       Normal
  Gradient mode                       Fast*

5/+
```

## 8.2.2. Design Matrix

Supplementary Figure 20: Design Matrix in SPM12 (Flexible-factorial analysis)



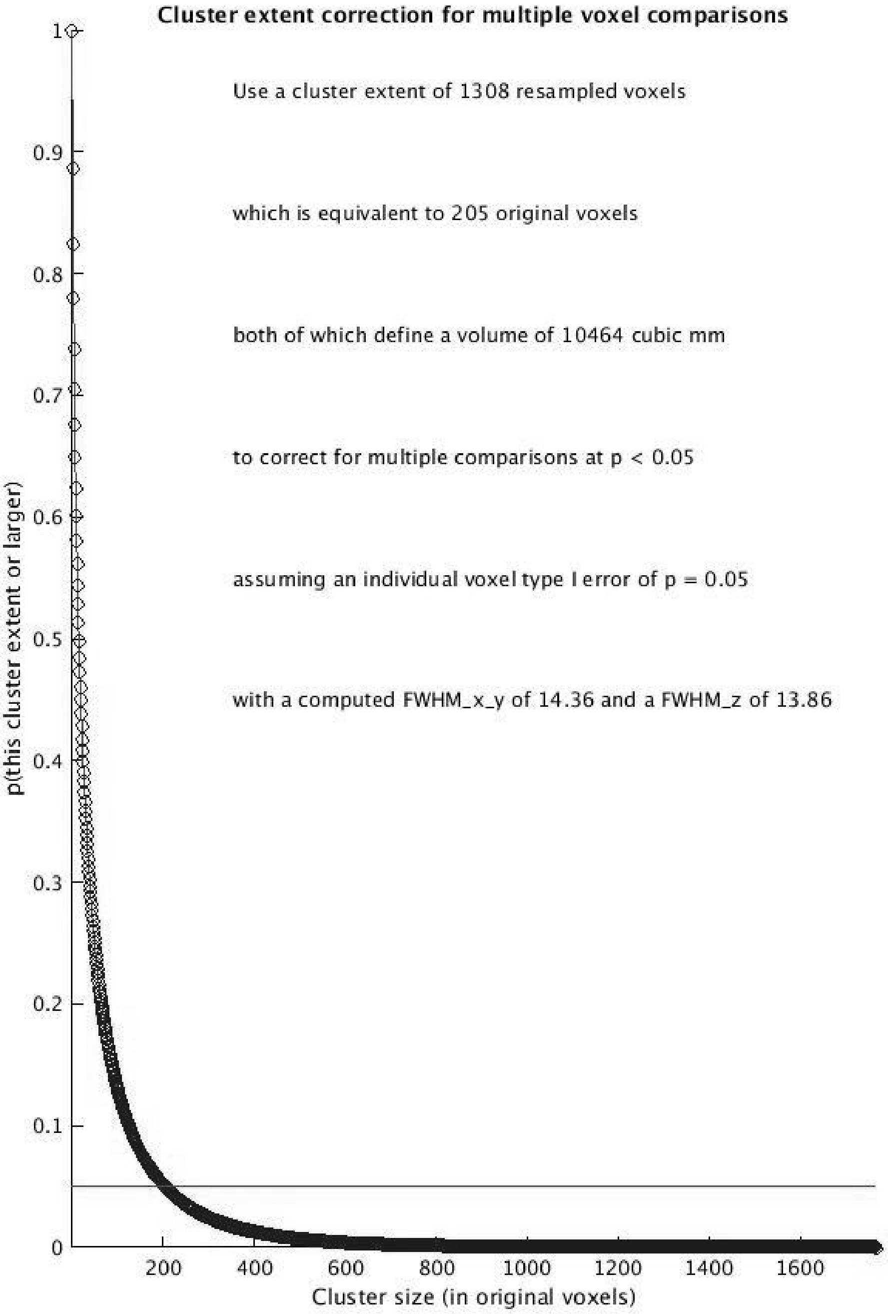
### Statistical analysis: Design

Design description...

```
                Design : Flexible factorial
    Global calculation : omit
   Grand mean scaling : <no grand Mean scaling>
Global normalisation : <no global normalisation>
            Parameters : 8 condition, +1 covariate, +0 block, +0 nuisance
                         9 total, having 9 degrees of freedom
                         leaving 303 degrees of freedom from 312 images
```

### 8.2.3. Monte-Carlo-Simulation

Supplementary Figure 35: Monte-Carlo-Simulation for minimal voxel contiguity threshold (Slotnick, 2017; Slotnick et al., 2003)



## 8.2.4. Declaration of informed consent

Klinik für Psychiatrie und Psychotherapie der
Philipps-Universität Marburg

Direktor: Prof. Dr. T. Kircher

Projektleiter:
PD Dr. B. Straube
Klinik für Psychiatrie und Psychotherapie der Philipps-Universität Marburg
Rudolf-Bultmann-Straße 8, 35039 Marburg
Tel: 06421-58-65200 (Sekr.: 58-66219)
Fax:06421-58-68939

### Einwilligungserklärung der Patienten zur Teilnahme an dem Forschungsvorhaben

„Untersuchung störungsspezifischer Unterschiede in den neuralen Korrelaten natürlicher sozial-kommunikativer Wahrnehmungsprozesse bei Patienten mit Schizophrenie, Depression und Bipolarer Störung"

**Bei Ihrer Bereitschaft zur Teilnahme bitten wir Sie, die Einwilligungserklärung vor der Untersuchung vollständig auszufüllen und zu unterschreiben.**

Ich bestätige hiermit, dass ich durch den Untersucher (Klinikmitarbeiter), Herrn/Frau ............................ mündlich über Wesen, Bedeutung, Risiken und Tragweite der beabsichtigten Studie aufgeklärt wurde und für meine Entscheidung genügend Bedenkzeit hatte.

Ich habe die Patienteninformation gelesen, ich fühle mich ausreichend informiert und habe verstanden, worum es geht. Der Untersucher hat mir ausreichend Gelegenheit gegeben, Fragen zu stellen, die alle für mich ausreichend beantwortet wurden. Ich hatte genügend Zeit mich zu entscheiden.

Ich wurde darauf hingewiesen, dass es sich bei der Studie um eine Forschungsstudie handelt. Eine neuroradiologische Befundung der MR-Bilder im Sinne einer klinisch orientierten Diagnostik findet daher nicht statt. Dennoch kann es vorkommen, dass in den MR-Bildern Signalauffälligkeiten entdeckt werden, die eine mögliche klinische Relevanz haben („Zufallsbefund"). Mir ist bekannt, dass der Versuchsleiter mich informieren würde, falls sich bei der Untersuchung Anhaltspunkte für einen Zufallsbefund ergeben, die eine fachärztliche neuro-radiologische Diagnostik empfehlenswert erscheinen lassen.

Ich habe verstanden, dass bei wissenschaftlichen Studien persönliche Daten und medizinische Befunde erhoben werden. Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie meine freiwillige Einwilligung voraus. Ich erkläre mich damit einverstanden, dass im Rahmen dieser Studie erhobene Daten auf Fragebögen und elektronischen Datenträgern aufgezeichnet und ohne Namensnennung zum Zwecke wissenschaftlicher Auswertung analysiert werden.

Ich habe eine Kopie der Probandeninformation und dieser unterschriebenen Einwilligungserklärung erhalten. Meine Einwilligung, an diesem Forschungsvorhaben als Proband teilzunehmen, erfolgt freiwillig. Ich wurde darauf hingewiesen, dass ich meine Einwilligung jederzeit ohne Angabe von Gründen und ohne Nachteile widerrufen kann.

**Ich willige hiermit ein, als Proband an dem Forschungsvorhaben, „Untersuchung störungsspezifischer Unterschiede in den neuralen Korrelaten natürlicher sozial-kommunikativer Wahrnehmungsprozesse bei Patienten mit Schizophrenie, Depression und Bipolarer Störung " teilzunehmen.**

VOM PROBANDEN AUSZUFÜLLEN:

Name: ……………………………..

Geburtsdatum: ………………………

Datum: …………………..

Ort: …………………………… Unterschrift: ……………………….

VOM UNTERSUCHER AUSZUFÜLLEN:

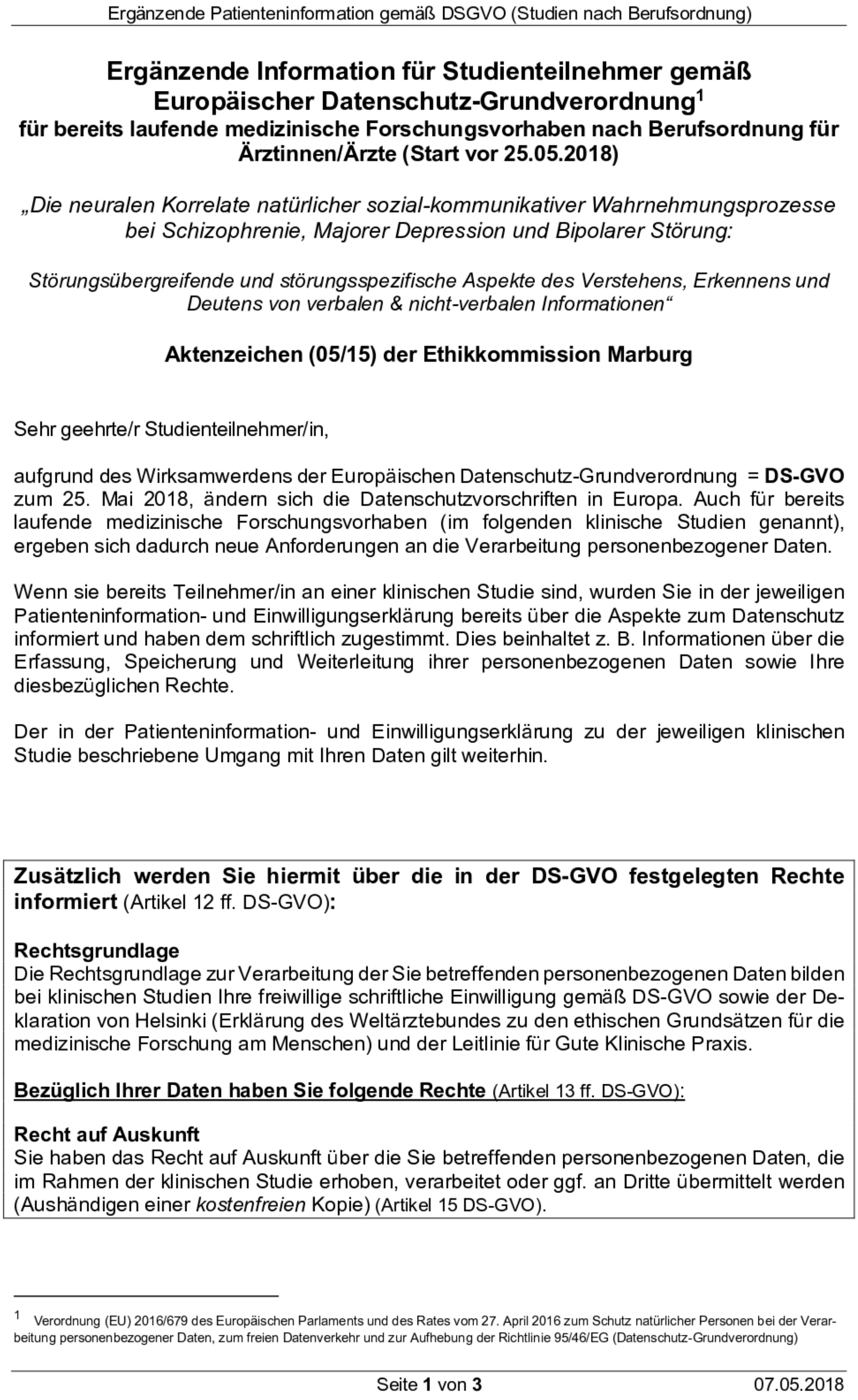
Ich habe den Probanden mündlich über Wesen, Bedeutung, Reichweite und Risiken des Forschungsvorhabens aufgeklärt.

Datum: ………………………..

Ort: ……………………………..

Untersucher: ………………………………………

## 8.2.5. Data privacy statement



# Ergänzende Information für Studienteilnehmer gemäß Europäischer Datenschutz-Grundverordnung[1]

### für bereits laufende medizinische Forschungsvorhaben nach Berufsordnung für Ärztinnen/Ärzte (Start vor 25.05.2018)

*„Die neuralen Korrelate natürlicher sozial-kommunikativer Wahrnehmungsprozesse bei Schizophrenie, Majorer Depression und Bipolarer Störung:*

*Störungsübergreifende und störungsspezifische Aspekte des Verstehens, Erkennens und Deutens von verbalen & nicht-verbalen Informationen“*

**Aktenzeichen (05/15) der Ethikkommission Marburg**

Sehr geehrte/r Studienteilnehmer/in,

aufgrund des Wirksamwerdens der Europäischen Datenschutz-Grundverordnung = **DS-GVO** zum 25. Mai 2018, ändern sich die Datenschutzvorschriften in Europa. Auch für bereits laufende medizinische Forschungsvorhaben (im folgenden klinische Studien genannt), ergeben sich dadurch neue Anforderungen an die Verarbeitung personenbezogener Daten.

Wenn sie bereits Teilnehmer/in an einer klinischen Studie sind, wurden Sie in der jeweiligen Patienteninformation- und Einwilligungserklärung bereits über die Aspekte zum Datenschutz informiert und haben dem schriftlich zugestimmt. Dies beinhaltet z. B. Informationen über die Erfassung, Speicherung und Weiterleitung ihrer personenbezogenen Daten sowie Ihre diesbezüglichen Rechte.

Der in der Patienteninformation- und Einwilligungserklärung zu der jeweiligen klinischen Studie beschriebene Umgang mit Ihren Daten gilt weiterhin.

**Zusätzlich werden Sie hiermit über die in der DS-GVO festgelegten Rechte informiert** (Artikel 12 ff. DS-GVO)**:**

**Rechtsgrundlage**
Die Rechtsgrundlage zur Verarbeitung der Sie betreffenden personenbezogenen Daten bilden bei klinischen Studien Ihre freiwillige schriftliche Einwilligung gemäß DS-GVO sowie der Deklaration von Helsinki (Erklärung des Weltärztebundes zu den ethischen Grundsätzen für die medizinische Forschung am Menschen) und der Leitlinie für Gute Klinische Praxis.

**Bezüglich Ihrer Daten haben Sie folgende Rechte** (Artikel 13 ff. DS-GVO):

**Recht auf Auskunft**
Sie haben das Recht auf Auskunft über die Sie betreffenden personenbezogenen Daten, die im Rahmen der klinischen Studie erhoben, verarbeitet oder ggf. an Dritte übermittelt werden (Aushändigen einer *kostenfreien* Kopie) (Artikel 15 DS-GVO).

---

[1] Verordnung (EU) 2016/679 des Europäischen Parlaments und des Rates vom 27. April 2016 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten, zum freien Datenverkehr und zur Aufhebung der Richtlinie 95/46/EG (Datenschutz-Grundverordnung)

**Recht auf Berichtigung**
Sie haben das Recht Sie betreffende unrichtigen personenbezogene Daten berichtigen zu lassen (Artikel 16 und 19 DS-GVO).

**Recht auf Löschung**
Sie haben das Recht auf Löschung Sie betreffender personenbezogener Daten, z. B. wenn diese Daten für den Zweck, für den sie erhoben wurden, nicht mehr notwendig sind (Artikel 17 und 19 DS-GVO).

**Recht auf Einschränkung der Verarbeitung**
Unter bestimmten Voraussetzungen haben Sie das Recht auf Einschränkung der Verarbeitung zu verlangen, d.h. die Daten dürfen nur gespeichert, nicht verarbeitet werden. Dies müssen Sie beantragen. Wenden Sie sich hierzu bitte an ihren Prüfer oder an den Datenschutzbeauftragten des Prüfzentrums (Artikel 18 und 19 DS-GVO).

**Im Falle Berichtigung, Löschung, Einschränkung der Verarbeitung** werden zudem all jene benachrichtigt, die ihre Daten haben (Artikel 17 (2) und Artikel 19 DS-GVO).

**Recht auf Datenübertragbarkeit**
Sie haben das Recht, die sie betreffenden personenbezogenen Daten, die sie dem Verantwortlichen für die klinische Studie / klinische Prüfung bereitgestellt haben, zu erhalten. Damit können Sie beantragen, dass diese Daten entweder Ihnen oder, soweit technisch möglich, einer anderen von Ihnen benannten Stelle übermittelt werden (Artikel 20 DS-GVO).

**Widerspruchsrecht**
Sie haben das Recht, jederzeit gegen konkrete Entscheidungen oder Maßnahmen zur Verarbeitung der Sie betreffenden personenbezogenen Daten Widerspruch einzulegen (Art 21 DSGVO). Eine solche Verarbeitung findet anschließend grundsätzlich nicht mehr statt.

**Einwilligung zur Verarbeitung personenbezogener Daten und Recht auf Widerruf dieser Einwilligung**
Die Verarbeitung ihrer personenbezogenen Daten ist nur mit Ihrer Einwilligung rechtmäßig (Artikel 6 DS-GVO).

Sie haben das Recht, ihre Einwilligung zur Verarbeitung personenbezogener Daten jederzeit zu widerrufen. Es dürfen jedoch die bis zu diesem Zeitpunkt erhobenen Daten durch die in der Patienteninformation- und Einwilligungserklärung zu der jeweiligen klinischen Studie / Prüfung genannten Stellen verarbeitet werden (Artikel 7, Absatz 3 DSGVO).

**Benachrichtigung bei Verletzung des Schutzes personenbezogener Daten („Datenschutzpannen“)**
Hat eine Verletzung des Schutzes personenbezogener Daten voraussichtlich ein hohes Risiko für Ihre persönlichen Rechte und Freiheiten zur Folge, so werden Sie unverzüglich benachrichtigt (Artikel 34 DSGVO).

**Möchten Sie eines dieser Rechte in Anspruch nehmen, wenden Sie sich bitte an** Ihren Prüfer oder an den Datenschutzbeauftragten Ihres Prüfzentrums. Außerdem haben Sie das **Recht, Beschwerde bei der/den Aufsichtsbehörde/n einzulegen,** wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DS-GVO verstößt (**siehe Kontaktdaten**).

## Kontaktdaten

### Datenschutz: Kontaktdaten Prüfzentrum

| **Datenschutzbeauftragte/r** | | **Datenschutz-Aufsichtsbehörde** | |
|---|---|---|---|
| ggf. Name: | Datenschutzbeauftragter der Philipps-Universität Marburg | ggf. Name: | Der Hessische Datenschutzbeauftragte |
| Adresse: | Biegenstraße 10<br>35032 Marburg<br>(Paketpost: 35037 Marburg) | Adresse: | Gustav-Stresemann-Ring 1<br>65189 Wiesbaden |
| Telefon: | 06421-2826155 | Telefon: | Telefon: 0611-140 80 |
| E-Mail | datenschutz@uni-marburg.de | E-Mail | poststelle@datenschutz.hessen.de |

| **Für die Datenverarbeitung Verantwortliche/r** | |
|---|---|
| ggf. Name | Benjamin Straube |
| Adresse: | Rudolf-Bultmann-Str. 8<br>35039 Marburg |
| Telefon: | 06421-58-61569 |
| E-Mail | straubeb@med.uni-marburg.de |

Eine **Unterschrift** ist **nur für ab dem 25.05.2018 neu eingeschlossenen Patienten** erforderlich, für bereits eingeschlossenen Patienten optional zur Bestätigung der Kenntnisnahme.

Name in Druckschrift ____________ Datum ____________ Unterschrift ____________

### 8.2.6. Sociodemographic questionnaire

## Anamnese

**Interviewer:** ____________________________________ **Datum:** __________

**Patient:** ________________________________________

**Muttersprache:** _____________________

## Soziodemographische Daten

**Alter:** ______ aktueller Beruf: ________________________________________

**Schulabschluss:**

| | |
|---|---|
| keinen | _ |
| Hauptschulabschluss | _ |
| mittlere Reife | _ |
| Fachabitur | _ |
| Abitur | _ |

Sonstiges _______________________________________________________________

Anzahl Schuljahre: ________

**Ausbildung (Mehrfachantwort möglich):**

| | | |
|---|---|---|
| keine | _ | |
| Ausbildung | _ | abgeschlossen **Ja** _ **Nein** _ |
| duale Ausbildung | _ | abgeschlossen **Ja** _ **Nein** _ |
| Fachhochschulstudium | _ | abgeschlossen **Ja** _ **Nein** _ |
| Hochschulstudium | _ | abgeschlossen **Ja** _ **Nein** _ |
| Promotion | _ | abgeschlossen **Ja** _ **Nein** _ |

Sonstiges _______________________________________________________________

**Raucher:** **Ja** _ **Nein** _ (falls ja, Menge an Zigaretten/Tag: ______)

**Händigkeit:** **rechts** _ **links** _

**zur Zeit in psychologischer Behandlung:** **Ja** _ **Nein** _

### 8.2.7. Follow-up questionnaire

Fragen zum Test:

**Als wie sehr zutreffend würden Sie folgende Aussagen bewerten:**

**Die Frage, ob ich mich angesprochen fühle, habe ich verstanden:**

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Es fiel mir leicht, die Fragen danach, ob ich mich angesprochen fühle, zu beantworten**:

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Die Frage, ob Gestik und Sprache zusammengepasst haben, habe ich verstanden:**

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Es fiel mir leicht, die Fragen nach der Passung von Gestik und Sprache zu beantworten**:

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Die Frage, ob es in dem Satz um Gefühle, Aufforderungen oder Bewertungen geht, habe ich verstanden:**

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Es fiel mir leicht, die Fragen, ob es in dem Satz um Gefühle, Aufforderungen oder Bewertungen geht, zu beantworten**:

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Ich habe mir viel Mühe gegeben, die Fragen richtig zu beantworten:**

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

**Der Schauspieler wirkt auf mich sehr sympathisch:**

1 2 3 4 5 6 7
Nicht zutreffend zutreffend

Kommentare:
______________________________________________________________________
______________________________________________________________________
______________________________________________________________________
______________________________________________________________________

## Vielen Dank für Ihre Teilnahme!

### 8.2.8. Multiple-Choice Word Test B (Lehrl et al., 1995)

## MWT - B

Anweisung:
Sie sehen hier mehrere Reihen mit Wörtern. In jeder Reihe steht **höchstens ein Wort**, das Ihnen vielleicht bekannt ist. Wenn Sie es gefunden haben, streichen Sie es bitte durch.

1 Nale - Sahe - Nase - Nesa - Sehna
2 Funktion - Kuntion - Finzahm - Tuntion - Tunkion
3 Struk - Streik - Sturk - Strek - Kreik
4 Kulinse - Kulerane - Kulisse - Klubihle - Kubistane
5 Kenekel - Gesonk - Kelume - Gelenk - Gelerge
6 siziol - salzahl - sozihl - sziam - sozial
7 Sympasie - Symmofeltrie - Symmantrie - Symphonie - Symplanie
8 Umma - Pamme - Nelle - Ampe - Amme
9 Krusse - Surke - Krustelle - Kruste - Struke
10 Kirse - Sirke - Krise - Krospe - Serise
11 Tinxur - Kukutur - Fraktan - Tinktur - Rimsuhr
12 Unfision - Fudision - Infusion - Syntusion - Nuridion
13 Feudasmus - Fonderismus - Föderalismus - Födismus - Föderasmus
14 Redor - Radium - Terion - Dramin - Orakium
15 kentern - knerte - kanzen - kretern - trekern
16 Kantate - Rakante - Kenture - Krutehne - Kallara
17 schalieren - waschieren - wakieren - schackieren - kaschieren
18 Tuhl - Lar - Lest - Dall - Lid
19 Dissonanz - Diskrisanz - Distranz - Dinotanz - Siodenz

20 Ferindo - Inferno - Orfina - Firanetto - Imfindio

21 Rilkiase - Kilister - Riliker - Klistier - Linkure

22 kurinesisch - kulinarisch - kumensisch - kulissarisch - kannastrisch

23 Rosto - Torso - Soro - Torgos - Tosor

24 Kleiber - Beikel - Keibel - Reikler - Biekerl

25 Ralke - Korre - Ruckse - Recke - Ulte

26 Lamone - Talane - Matrone - Tarone - Malonte

27 Tuma - Umat - Maut - Taum - Muta

28 Sorekin - Sarowin - Rosakin - Narosin - Kerosin

29 beralen - gerältet - anälteren - untären - verbrämen

30 Kapaun - Paukan - Naupack - Aupeck - Ankepran

31 Sickaber - Bassiker - Kassiber - Sassiker - Askiber

32 Pucker - Keuper - Eucker - Reuspeck - Urkane

33 Spirine - Saprin - Parsin - Purin - Asprint

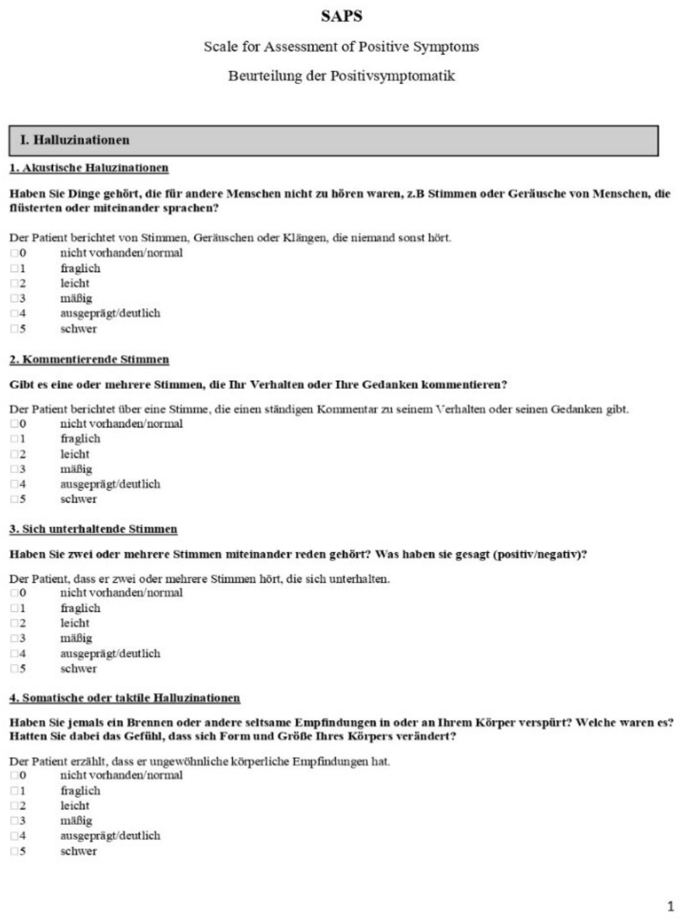
34 Kulon - Solgun - Koskan - Soran - Klonus

35 Adept - Padet - Edapt - Epatt - Taped

36 Gindelat - Tingerat - Indigenat - Nitgesaar - Ringelaar

37 Berkizia - Brekzie - Birakize - Brikazie - Bakiria

## 8.2.9. Scale for Assessment of Positive Symptoms (N. Andreasen, 1984b) and Scale for Assessment of Negative Symptoms (N. Andreasen, 1984a)



### SAPS

Scale for Assessment of Positive Symptoms

Beurteilung der Positivsymptomatik

**I. Halluzinationen**

**1. Akustische Haluzinationen**

**Haben Sie Dinge gehört, die für andere Menschen nicht zu hören waren, z.B Stimmen oder Geräusche von Menschen, die flüsterten oder miteinander sprachen?**

Der Patient berichtet von Stimmen, Geräuschen oder Klängen, die niemand sonst hört.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**2. Kommentierende Stimmen**

**Gibt es eine oder mehrere Stimmen, die Ihr Verhalten oder Ihre Gedanken kommentieren?**

Der Patient berichtet über eine Stimme, die einen ständigen Kommentar zu seinem Verhalten oder seinen Gedanken gibt.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**3. Sich unterhaltende Stimmen**

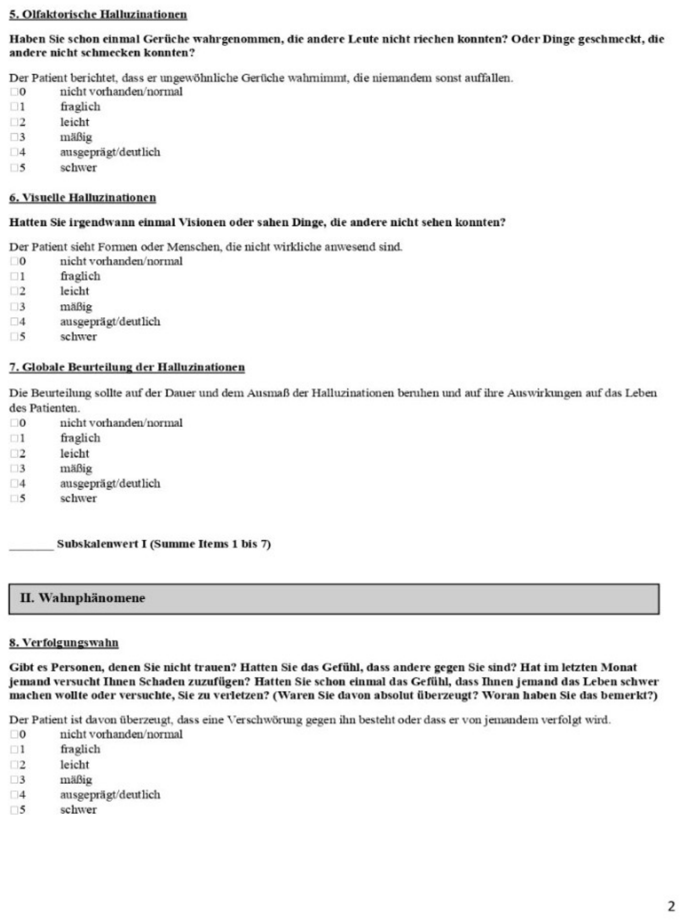
**Haben Sie zwei oder mehrere Stimmen miteinander reden gehört? Was haben sie gesagt (positiv/negativ)?**

Der Patient, dass er zwei oder mehrere Stimmen hört, die sich unterhalten.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**4. Somatische oder taktile Halluzinationen**

**Haben Sie jemals ein Brennen oder andere seltsame Empfindungen in oder an Ihrem Körper verspürt? Welche waren es? Hatten Sie dabei das Gefühl, dass sich Form und Größe Ihres Körpers verändert?**

Der Patient erzählt, dass er ungewöhnliche körperliche Empfindungen hat.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer



**5. Olfaktorische Halluzinationen**

**Haben Sie schon einmal Gerüche wahrgenommen, die andere Leute nicht riechen konnten? Oder Dinge geschmeckt, die andere nicht schmecken konnten?**

Der Patient berichtet, dass er ungewöhnliche Gerüche wahrnimmt, die niemandem sonst auffallen.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**6. Visuelle Halluzinationen**

**Hatten Sie irgendwann einmal Visionen oder sahen Dinge, die andere nicht sehen konnten?**

Der Patient sieht Formen oder Menschen, die nicht wirkliche anwesend sind.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**7. Globale Beurteilung der Halluzinationen**

Die Beurteilung sollte auf der Dauer und dem Ausmaß der Halluzinationen beruhen und auf ihre Auswirkungen auf das Leben des Patienten.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

_______ **Subskalenwert I (Summe Items 1 bis 7)**

**II. Wahnphänomene**

**8. Verfolgungswahn**

**Gibt es Personen, denen Sie nicht trauen? Hatten Sie das Gefühl, dass andere gegen Sie sind? Hat im letzten Monat jemand versucht Ihnen Schaden zuzufügen? Hatten Sie schon einmal das Gefühl, dass Ihnen jemand das Leben schwer machen wollte oder versuchte, Sie zu verletzen? (Waren Sie davon absolut überzeugt? Woran haben Sie das bemerkt?)**

Der Patient ist davon überzeugt, dass eine Verschwörung gegen ihn besteht oder dass er von jemandem verfolgt wird.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 9. Eifersuchtswahn

**Haben Sie eine(n) Partner(in)? Wenn ja: Wie ist das Verhältnis? Haben Sie einmal befürchtet, dass Ihr Partner untreu war? Welche Beweise hatten Sie?**

Der Patient ist davon überzeugt, dass sein Partner eine Affäre mit einem anderen hat.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 10. Wahnvorstellungen von Schuld oder Sühne

**Hatten Sie jemals das Gefühl, etwas Schreckliches getan zu haben, wofür Sie eine Strafe verdienen?**

Der Patient ist davon überzeugt, dass er eine furchtbare Sünde begangen hat, die nicht vergeben werden kann.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 11. Größenideen

**Sind Sie ein ungewöhnlicher Mensch? Hatten Sie jemals das Gefühl, dass Sie in irgendeiner Weise besonders wichtig waren oder dass Sie über spezielle Kräfte verfügten, um Dinge zu tun, die andere nicht tun konnten?**

Der Patient ist davon überzeugt, dass er besondere Fähigkeiten oder Macht besitzt.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 12. Religiöse Wahnvorstellung

**Haben Sie jemals irgendwelche ungewöhnlichen religiösen Erfahrungen gemacht?**

Der Patient beschäftigt sich intensiv mit Wahnvorstellungen religiöser Natur.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 13. Körperbezogener Wahn

**Hatten Sie jemals das Gefühl, dass irgendetwas körperlich mit Ihnen nicht stimmte, obwohl Ihnen ihr Arzt nach sorgfältiger Untersuchung versicherte, dass alles in Ordnung ist? Kam es Ihnen jemals so vor, als ob etwas Seltsames mit Ihrem Körper geschieht oder gibt es etwas an ihm, was krank oder abnormal ist?**

Der Patient ist davon überzeugt, dass sein Körper irgendwie krank, abnorm oder verändert ist.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht

☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 14. Beziehungsideen

**Hatten Sie jemals beim Betreten des Raums das Gefühl, dass Menschen über Sie sprechen? Wenn ja: Waren Sie überzeugt, dass die Leute über Sie geredet haben oder haben Sie es sich nur eingebildet? Erhielten Sie jemals spezielle Botschaften über Radio, Fernsehen, Zeitung oder durch die Art und Weise, wie die Dinge um Sie herum angeordnet sind?**

Der Patient ist davon überzeugt, dass unbedeutende Bemerkungen oder Ereignisse sich auf ihn beziehen oder eine besondere Bedeutung haben.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 15. Wahn, kontrolliert zu werden

**Waren Sie jemals davon überzeugt, dass jemand oder irgendeine Kraft oder Macht von außen Ihre Gedanken, Gefühle oder Handlungen beeinflusste oder steuerte?**

Der Patient hat den Eindruck, dass seine Gefühle oder Handlungen durch eine fremde Macht kontrolliert werden.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 16. Wahn, dass Gedanken gelesen werden

**Hatten Sie jemals das Gefühl, dass andere Menschen Ihre Gedanken lesen konnten?**

Der Patient hat den Eindruck, dass andere Menschen seine Gedanken lesen können oder seine Gedanken kennen.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 17. Gedankenausbreitung

**Waren Sie jemals davon überzeugt, dass Ihre Gedanken laut nach außen übertragen wurden, so dass andere Leute wirklich hören konnten, was Sie dachten?**

Der Patient ist davon überzeugt, dass seine Gedanken ausstrahlt werden, so dass sie von ihm oder anderen gehört werden können.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**18. Gedankeneingebung**

**Hatten Sie das Gefühl, dass Ihnen bestimmte Gedanken, die nicht Ihre eigenen waren, direkt eingegeben wurden?**

Der Patient ist davon überzeugt, dass ihm fremde Gedanken eingegeben werden.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**19. Gedankenentzug**

**Hatten Sie das Gefühl, dass Ihnen bestimmte Gedanken entzogen wurden?**

Der Patient ist davon überzeugt, dass ihm Gedanken entzogen werden.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**20. Globale Beurteilung der Wahnphänomene**

Die Beurteilung sollte auf der Dauer und dem Ausmaß der Wahnphänomene beruhen und auf ihre Auswirkungen auf das Leben des Patienten.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

_______ **Subskalenwert II (Summe Items 8 bis 20)**

## III. Bizarres Verhalten

**21. Kleidung und Erscheinungsbild**

Der Patient kleidet sich in ungewöhnlicher Weise oder unternimmt etwas Ungewöhnliches, um sein Erscheinungsbild zu verändern.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**22. Soziales und sexuelles Verhalten**

Der Patient führt Handlungen aus, die nach den üblichen sozialen Normen als unangemessen angesehen werden (z.B. Masturbation in der Öffentlichkeit).
☐0 nicht vorhanden/normal

☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**23. Aggressives und agitiertes Verhalten**

Der Patient verhält sich, in einer häufigen und unvorhersehbaren Weise, aggressiv und agitiert.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**24. Repetitives oder stereotypes Verhalten**

Der Patient entwickelt eine Anzahl repetitiver Handlungen oder Rituale, die er ständig durchfahren muss.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

**25. Globale Beurteilung des bizarren Verhaltens**

Diese Beurteilung sollte die Art des Verhaltens und das Ausmaß, in dem es von den sozialen Normen abweicht, wiedergeben.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

_______ **Subskalenwert III (Summe Items 21 bis 25)**

## IV Positive formale Denkstörung

**26. Entgleisung**

Eine Form der Sprache, bei der die Vorstellung zu Ideen ableiten, die mit den ursprünglichen nur noch entfernt zu tun haben oder davon abhängig sind.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 27. Tangentialität

Die Beantwortung einer Frage in einer willkürlichen oder irrelevanten Weise.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 28. Inkohärenz

Eine Form der Sprache, die manchmal völlig unverständlich ist.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 29. Unlogisches Denken

Eine Form der Sprache, in der es zu Schlussfolgerungen kommt, die keiner Logik folgen.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 30. Umständlichkeit

Eine Form der Sprache, die seht indirekt ist und erst nach erheblicher Zeit zum Kern kommt.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 31. Rededrang

Der Patient spricht schnell und ist schwer zu unterbrechen. Die Sprachproduktion ist höher als normal.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 32. Ablenkbarkeit

Der Patient wird durch Reize in der Umgebung leicht abgelenkt und dadurch in seinem Sprachfluss unterbrochen.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich

☐5 schwer

### 33. Klangassoziationen

Eine Form der Sprache, bei der eher der Klang als eine sinnvolle Beziehung die Wortwahl steuern.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

### 34. Globale Beurteilung der positiven Denkstörung

Diese Beurteilung sollte die Häufigkeit der Abweichung vom Normalen und das Ausmaß, in der sie die Kommunikationsfähigkeit des Patienten beeinträchtigt, umfassen.
☐0 nicht vorhanden/normal
☐1 fraglich
☐2 leicht
☐3 mäßig
☐4 ausgeprägt/deutlich
☐5 schwer

_______ **Subskalenwert IV (Summe Items 26 bis 34)**

## V Unangemessener Affekt

### 35. Unangemessener Affekt

Der Affekt des Patienten ist unangemessen oder inkongruent, nicht lediglich abgeflacht oder abgestumpft.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

_______ **Symptomwert V (Items 35)**

_______ **Summe der Globalratings (Items 7, 20, 25 und 34)**

_______ **Erweiterter Summenscore (Items 7, 20, 25 und 34 sowie Item 35)**

_______ **Gesamtskalenwert (Subskalenwert I, II, III, IV)**

_______ **Erweiterter Gesamtskalenwert (Subskalenwert I, II, III, IV sowie Item 35)**

# SANS

## Scale for Assessment of Negative Symptoms

## Beurteilung der Minussymptomatik

### I Affektverflachung und Affektstarrheit

Affektverflachung und Affektstarrheit manifestiert sich als eine charakteristische Verarmung der emotionalen Ausdrucksfähigkeit und des Fühlens.
Zur Beurteilung der nachfolgenden Items sollten normalerweise affektbesetzte Themen zur Sprache gebracht werden.

#### 1. Starrer Gesichtsausdruck

Das Gesicht des Patienten erscheint hölzern, mechanisch, gefroren. Der Gesichtsausdruck wechselt nicht oder weniger als es der gefühlsmäßige Inhalt des Gesprächs erwarten lässt. Der Neuroleptika teilweise diesen Effekt nachahmen, sollte der Beurteiler sorgfältig festhalten, ob der Patient eine neuroleptische Medikation erhält, aber nicht versuchen, die Beurteilung dieses Symptoms diesem Neuroleptika bedingten Effekt entsprechend anzupassen.

☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

#### 2. Verminderte Spontanbewegungen

Der Patient sitzt während des Gesprächs ruhig da und zeigt wenig oder keine Spontanbewegungen. Er wechselt seine Sitzung nicht, bewegt Beine oder Hände nicht oder weniger als normalerweise erwartet würde.

☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

#### 3. Armut und Ausdrucksbewegung

Der Patient verwendet seinen Körper nicht als Hilfsmittel um sich auszudrücken, wie z.B. Handbewegungen, sich vorlehnen im Stuhl oder entspanntes Zurücklehnen. Dies ist zusätzlich zu verminderten Spontanbewegungen zu beurteilen.

☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

#### 4. Geringer Augenkontakt

Der Patient vermeidet Blickkontakt während des Gesprächs oder die Augenpartie lässt keine Expressionen erkennen. Er scheint ins weite zu starren, selbst dann, wenn er spricht.

☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar

☐5 Gravierender Ausprägungsgrad

#### 5. Fehlende affektive Reaktionsfähigkeiten (Affektstarrheit)

Der Patient reagiert nicht, oder nicht ausreichend auf Gesprächsinhalte, die normalerweise mit heiterem oder traurigem Affekt beantwortet werden. Unfähigkeit zu lachen oder zu lächeln, wenn evoziert. Das kann geprüft werden, indem man lacht oder in einer Weise Witze macht, sodass man von einem normalen Menschen ein Lachen hervorrufen würde. Der Prüfer kann ebenso fragen, „Haben Sie vergessen zu lachen?“, während er selbst lächelt.

☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

#### 6. Mangel an vokaler Ausdrucksfähigkeit (monotone Sprache)

Beim Sprechen gelingt es dem Patienten nicht, ein normales Betonungsschema der Stimme zu zeigen. Wichtige Worte sind nicht durch Wechseln in Tonhöhe und Tonstärke charakterisierbar. Keine Modulation der Lautstärke bei vertraulichen oder allgemein interessierenden Gesprächsinhalten.

☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

#### 7. Globale Beurteilung der affektiven Verflachung

Die Globalbeurteilung sollte sich auf den allgemeinen Schweregrad der Affektverflachung und Affektstarrheit beziehen. Besondere Bedeutung sollten Hauptmerkmalen, wie mangelnder Auslenkbarkeit, Inadäquatheit und die allgemeine Verminderung der emotionalen Intensität gegeben werden.

☐0 normaler Affekt
☐1 fragliche affektive Verminderung
☐2 leichte affektive Verminderung
☐3 mäßige affektive Verminderung
☐4 deutliche affektive Verminderung
☐5 schwere Affektverflachung und Affektstarrheit

_______ **Subskalenwert I (Summe Items 1 bis 7)**

### II Alogie und Paralogie

Alogie beschreibt die Verarmung des Denkens und der Wahrnehmung, wie man sie bei schizophrenen Patienten findet. Der Denkprozess wirkt leer, verworren und langsam. Alogie manifestiert sich in einer stockenden, leeren Sprache (Armut der Sprache) oder in einer flüssigen, aber inhaltsleeren Sprache (Verarmung des Gesprächsinhaltes) und/oder erhöhter Antwortlatenz.

#### 8. Verarmung der Sprechweise

Es handelt sich um eine Verminderung in der Menge des spontanen Gesprächs, sodass die Antworten zu Fragen dazu tendieren, kurz, konkret und unausgearbeitet zu sein. Ungefragte zusätzliche Informationen werden spärlich gegeben.
**Beispiel:** Frage: „Wie viele Kinder haben Sie?“ Antwort: „2, ein Bub und ein Mädchen, das Mädchen ist 13 und der Bub ist 10.“ – „2“ wäre alles, was zur Beantwortung erforderlich ist und der Rest ist zusätzliche Information. Antworten können auch einsilbig sein. Manche Fragen können unbeantwortet bleiben. Wenn der Interviewer mit dieser Sprechweise konfrontiert wird, kann er sich oft dabei ertappen, nachzufragen, um den Patienten in der Ausarbeitung von Antworten zu ermuntern. Um diesen

Befund ans Licht zu bringen, muss der Prüfer dem Patienten ausreichend Zeit zur Beantwortung bzw. seine Antwort auszuarbeiten zur Verfügung stellen

☐0 keine Verarmung; eine substantielle und entsprechende Anzahl von Antworten auf Fragen enthalten zusätzliche Informationen
☐1 fragliche Verarmung
☐2 leichte Verarmung; gelegentliche Antworten enthalten keine ausführliche Information, selbst wenn dies angebracht ist
☐3 mäßige Verarmung der Sprache; einige Antworten enthalten eine geeignete zusätzliche Information, viele Antworten sind einsilbig und sehr kurz (z.B. „Ja“, „Nein“, „Vielleicht“, „Letzte Woche“ etc.)
☐4 deutliche Sprachverarmung; Antworten sind selten länger als einige Worte
☐5 schwere Verarmung; Patient sagt sehr wenig und gelegentlich gelingt es ihm nicht zu antworten

### 9. Verarmung des Gesprächsgehaltes (Gesprächsinhalt)

Obwohl die Antworten adäquat sind, enthalten sie nur wenige Informationen. Die Sprache tendiert zu Unbestimmtheit, oft überabstrakt und überkonkret, wiederholend und stereotyp. Der Interviewer kann diesen Befund durch die Beobachtung erkennen, nämlich dass der Patient zwar lange gesprochen hat, aber ohne adäquate Informationen zur Beantwortung der Frage. Andererseits kann der Patient genug Informationen liefern, doch er benötigt dazu eine übermäßige Anzahl von Worten, obwohl die Antwort in ein bis zwei Sätzen subsummiert werden könnte. Manchmal kann man diese Sprechweise auch als „leeres philosophieren“ charakterisieren. Ausschluss: Unterschied zur Weitschweifigkeit, da der weitschweifige Patient dazu tendiert, eine Fülle von Detailinformationen zu liefern.

☐0 keine Verarmung
☐1 fragliche Verarmung
☐2 leichte Verarmung; gelegentliche Antworten sind zu unklar, um begreiflich zu sein oder die Antwort könnte merklich gestrafft werden
☐3 mäßige Verarmung; häufig sind Antworten unklar oder könnten merklich gestrafft werden, um das Gespräch auf mindestens ¼ zu verkürzen
☐4 merkliche Verarmung; mindestens die Hälfte des Gesprächs ist davon betroffen
☐5 schwer, nahezu das gesamte Gespräch ist unklar und/oder unfassbar

### 10. Sperrungen

Unterbrechungen des Sprachduktus, bevor ein Gedanke oder eine Idee vollendet wurde. Nach einer gewissen Schweigezeit, welche von wenigen Minuten bis Sekunden dauern kann, gibt der Patient an, dass er nicht mehr abrufen kann, was er vorhatte zu sagen oder was er meinte zu sagen. Sperrungen sollten nur dann als vorhanden beurteilt werden, wenn der Patient freiwillig das „Verlieren seiner Gedanken“ beschreibt, oder wenn der Patient auf die Frage des Interviewers angibt, dass dies der Grund für seine Pause war.

☐0 keine Sperrungen
☐1 fraglich
☐2 leichte Sperrungen; einmaliges Auftreten während 15 Minuten
☐3 mäßige Sperrungen; zweimaliges Auftreten während 15 Minuten
☐4 merkliche Sperrungen; dreimaliges Auftreten während 15 Minuten
☐5 schwere Sperrungen; mehr als dreimaliges Vorkommen

### 11. Erhöhte Antwortlatenz

Der Patient braucht unverhältnismäßig lange, um Fragen zu beantworten. Bei Nachfragen zeigt sich jedoch, dass der Patient die Frage aufgefasst hat, es ihm aber schwerfällt, seine Gedanken zu entwickeln.

☐0 nicht vorhanden
☐1 fraglich
☐2 manchmal Pausen, kurz bevor der Patient antwortet
☐3 deutliche Pausen
☐4 ausgeprägte Verlängerung der Antwortlatenz
☐5 lange Pausen vor nahezu allen Antworten oder der Patient kann kaum antworten

### 12. Globale Beurteilung der Alogie

Da der Kernbefund von Alogie der Verarmung des Sprechend und des Gesprächsinhaltes sind, sollte die globale Beurteilung besonders diesem Umstand Rechnung tragen.

☐0 normaler Affekt
☐1 fragliche affektive Verminderung
☐2 leichte affektive Verminderung
☐3 mäßige affektive Verminderung
☐4 deutliche affektive Verminderung
☐5 schwere Affektverflachung und Affektstarrheit

_______ **Subskalenwert II (Summe Items 8 bis 12)**

## III Abulie und Apathie

Abulie manifestiert sich als ein charakteristischer Mangel an Energie, Antrieb und Interesse. Gelegentlich sind die Patienten von außen anregbar, bei Wegfall der Anregung erlischt der Antrieb jedoch rasch.

### 13. Pflege und Hygiene

**Können Sie sich selbst pflegen oder benötigen Sie Hilfe? Wie beurteilen Sie selbst Ihr äußeres Erscheinungsbild?**

Der Patient widmet seiner Pflege und Hygiene wenig Aufmerksamkeit, er muss zur Körperpflege angehalten werden.

☐0 nicht vorhanden
☐1 fraglich
☐2 leichte, aber sichere Anzeichen von Nachlässigkeit
☐3 unordentliche Erscheinung; der Patient muss gelegentlich zur Körperpflege angehalten werden
☐4 deutlich unordentliche Erscheinung; der Patient muss regelmäßig zur Körperpflege angehalten werden
☐5 extrem unordentlich und ungepflegt

### 14. Unstetigkeit in Beruf und Ausbildung

**Gehen Sie gerne zu den Therapieangeboten? Für ambulante Patienten: Wie sieht ihr Tagesablauf aus? Haben Sie aktuell eine geregelte Arbeit oder möchten diese wieder nachgehen? Gehen Sie häufig raus?**

Der Patient geht keiner geregelten Arbeit nach und/oder zeigt in dieser Richtung Verantwortungslosigkeit. Bei stationären Patienten: Der Patient muss zur Arbeits- und Beschäftigungstherapie angehalten werden oder weigert sich dorthin zu gehen.

☐0 nicht vorhanden
☐1 fraglich
☐2 leichte Anzeichen von Unstetigkeit
☐3 mäßige Anzeichen; der Patient muss gelegentlich dazu angehalten werden
☐4 merkliche Anzeichen; der Patient muss regelmäßig dazu angehalten werden
☐5 dem Patienten gelingt es nicht, Arbeit und Beschäftigung konsequent durchzuführen

### 15. Körperliche Energielosigkeit

Der Patient neigt zu körperlicher Trägheit. Er sitzt stundenlang im Stuhl und unternimmt keine spontanen Aktivitäten. Die meiste Zeit verbringt er mit passiven Tätigkeiten, wie z.B. Fernsehen etc. oder er ist untätig.

☐0 nicht vorhanden
☐1 fraglich
☐2 leichte Energielosigkeit

☐3 mäßig; der Patient muss gelegentlich zu Aktivitäten angehalten werden
☐4 der Patient muss regelmäßig zu Aktivitäten angehalten werden
☐5 der Patient verhält sich die meiste Zeit völlig passiv

**<u>16. Globale Beurteilung der Willensschwäche – Apathie</u>**

Die Beurteilung sollte des allgemeinen Schweregrad der Abulie-Symptomatik reflektieren, wo bei den vorhandenen, zu erwartenden Umständen, der soziale Status und der Herkunft des Patienten entsprochen werden sollte. Bei der Durchführung der Globalbeurteilung sollte ein starkes Gewicht zu ein oder zwei hervorstechenden Symptomen, wenn sie speziell zutreffen gegeben werden.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

_______ **Subskalenwert III (Summe Items 13 bis 16)**

**IV Anhedonie - Ungeselligkeit**

Dieser Symptomkomplex beinhaltet die Schwierigkeiten des Patienten Interesse und/oder Vergnügen zu empfinden. Dies kann sich in Interessenverlust an angenehmen Aktivitäten und/oder Unfähigkeiten bei solchen Aktivitäten Vergnügen zu empfinden, äußern und/oder als Desinteresse an sozialen Beziehungen verschiedenster Art.

**<u>17. Freizeitvergnügen und Aktivitäten</u>**

**Gibt es Dinge, mit denen Sie sich in Ihrer Freizeit immer wieder gerne beschäftigen? Wie viel Zeit wenden Sie dafür auf?**

Der Patient hat weniger oder keine Interessen, Aktivitäten oder Hobbies. Obwohl dieses Symptom langsam oder schleichend beginnen kann, wird man im Alltag ein eindeutiges Desinteresse an früheren Aktivitätsniveaus bemerken.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

**<u>18. Sexuelles Interesse</u>**

**Bei manchen Patienten nimmt das sexuelle Interesse ab, darf ich Ihnen die Frage stellen, wie es bei da Ihnen aussieht?**

Beurteilt werden soll das Interesse und die Bereitschaft sexuellen Kontakt aufzunehmen.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

**<u>19. Fähigkeit, Intimität und Nähe zu fühlen</u>**

**Leben Sie in einer Partnerschaft? Wie sieht Ihre Bereitschaft aus, Intimität und Nähe zu Ihrem Partner zu spüren?**

Beurteilt werden soll die Fähigkeit, zu einer Kontaktperson eine persönliche Beziehung aufzubauen und aufrechtzuerhalten.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

**<u>20. Verhalten zu Verwandten und Kollegen (Autismus)</u>**

**Wie schätzen Sie Ihre familiäre Situation ein? Haben Sie enge Freunde? Wie zufrieden sind Sie mit Ihren Freundschaften?**

Beurteilt werden soll die Fähigkeit des Patienten, in seinem sozialen Umfeld Kontakte zu knüpfen. Autistische Patienten nehmen spontan keine Kontakte auf; wenn man sie dazu anregt reagieren sie entweder gereizt oder versinken bei Wegfall der Anregung wieder in den alten Zustand.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

**<u>21. Globale Beurteilung der Anhedonie – Ungeselligkeit</u>**

Die Globalbeurteilung sollte den allgemeinen Schweregrad der Anhedonie-Komplexes reflektieren.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

_______ **Subskalenwert IV (Summe Items 17 bis 21)**

**V Aufmerksamkeit**

Die Aufmerksamkeit ist bei Schizophrenen oft gestört. Der Patient ist nicht fähig, seine Aufmerksamkeit auf etwas Bestimmtes zu konzentrieren und/oder er ist lediglich fähig, sich sporadisch und sprunghaft zu konzentrieren.

**<u>22. Soziale Unaufmerksamkeit</u>**

Der Patient hat von sich aus kein Interesse an sozialen Aktivitäten. Diese Interessenlosigkeit kann ich u.a. in negativistischem Verhalten äußern und/oder Versuche, an sozialen Aktivitäten teilzunehmen, scheitern an der mangelnden Konzentrationsfähigkeit.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

**23. Unaufmerksamkeit während psychologischer Testung**

Bei einmaliger Anwendung der Skala sollte der Mini-Mental-Status-Test (MMST) durchgeführt werden; dieser Test kann nach ca. 3 bis 4 Wochen wiederholt werden:
Bei regelmäßiger Anwendung und zur Beurteilung des Therapieerfolges sollte folgendermaßen vorgegangen werden:
- Wiederholung nach 1 Woche: 7 von 100 abziehen lassen
- Wiederholung nach 2 Wochen: 4-stellige Zahl rückwärts
- Wiederholung nach 3 Wochen: 9 von 100 abziehen lassen

Bei Untersuchungsende MMST
☐0 kein Fehler
☐1 fraglich (Patient führt die Aufgabe in zögernder Weise aus und/oder macht einen Fehler, den er sofort korrigiert)
☐2 1 Fehler
☐3 2 Fehler
☐4 3 Fehler
☐5 mehr als 3 Fehler

**24. Globale Beurteilung der Aufmerksamkeit**

Beurteilt werden soll die Aufmerksamkeit und Konzentrationsfähigkeit, wobei sowohl das klinische Bild sowie die Ausführung von Aufgaben in Betracht gezogen werden soll.
☐0 normal
☐1 Der pathologische Charakter des beobachteten Phänomens ist zweifelhaft
☐2 Diskret pathologische Ausprägung
☐3 Pathologische Ausprägung erkennbar
☐4 Pathologische Ausprägung für jeden Beobachter erkennbar
☐5 Gravierender Ausprägungsgrad

_______ **Subskalenwert V (Summe Items 22 bis 24)**

_______ **Summe der Globalratings (Item 7, 12, 16, 21, 24)**

_______ **Gesamtskalenwert (Subskalenwert I, II, III, IV, V)**

## 8.3. Index of academic teachers

My academic teachers in Marburg were:

Adamkiewicz, Aigner, Baranovski, Bartsch, Bauer, Becker, Becker, Bertoune, Bette, Bien, Birk, Bliemel, Bonaterra, Bösner, Brandt, Brehm, Cetin, Decher, Del Rey, Denkert, Donner-Banzhoff, Duda, Eberhart, Eggers, Engenhart-Cabillic, Ermisch, Feuser, Geks, Geraedts, Görg, Gress, Greulich, Günther, Halaszovich, Hertl, Hildebrandt, Hofmann, Hoyer, Jansen, Kalder, Kann, Kinscherf, Kirschbaum, Kircher, Koehler, Köhler, Kühnert, Lill, Lohoff, Lüsebrink, Luster, Mahnken, Maier, Maisner, Meißner, Mirow, Moll, Mutters, Nenadić, Neubauer, Neumüller, Oberwinkler, Oliver, Pagenstecher, Parahuleva, Plant, Preisig-Müller, Pfützner, Rastan, Reese, Renigunta, Renke, Renz, Ruchholtz, Sahmland, Schäfer, Schieffer, Schratt, Schröder, Schütz, Sekundo, Sevinc, Sommer, Stahl, Steiniger, Stiewe, Stuck, Tackenberg, Thieme, Timmermann, Vogelmeier, Wagner, Weihe, Westermann, Wiesmann, Wilhelm, Worzfeld, Wrocklage, Wulf, Ziller

# 8.4. Acknowledgements

This work was made possible by the help and cooperation of many people of which I would like to name a few.

First and foremost, I want to thank my supervisor, Prof. Dr. Benjamin Straube, for giving me the opportunity to take part in the GPLUS and G3 projects, and introducing me to a remarkable field of research. I am very grateful for the continuous guidance and excellent support, especially during the process of publication.

Also, great thanks go to Ms. Lydia Riedl, who was a brilliant project leader, mentor, and friend to me who kept me motivated with her own passion for research. Thank you for the fun teachings, the impeccable support and the lifesaving chocolate supplies.

Furthermore, I would like to thank Ms. Miriam Steines, without whom this thesis would not have been possible. Thank you for your fantastic help with quality control, data analysis and writing, which really elevated the quality of the paper. Thanks to Amelie Heitzmann for language editing of the published article.

Furthermore, I would also like to thank the G3 project team and principal investigator Prof. Dr. Arne Nagels for providing the data for this thesis. Many thanks go to the Core Facility Brain Imaging, Ms. Mechthild Wallnig and Ms. Rita Werner, for assistance with data collection and to Dr. Jens Sommer for technical support. I further thank Dr. Florian Bitsch for the competent assistance with all the “little questions”.

I would like to thank my friends and colleagues of the GPLUS project team, Annika, Anne, Chiara, and Maxi for the great times working together.

In addition, many thanks go to the German Scholarship Foundation for funding my medical studies.

Finally, I thank my family and my partner for supporting me during all these years.

Momoko Choudhury
Marburg 2023