FACE PROCESSING AND PREDICTION IN SCHIZOPHRENIA

A functional MRI study on repetition probability modulation of repetition suppression

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von Lisa Mareike Münke

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Gutachter:

1. Prof. Dr. Igor Nenadić (Universitätsklinikum Marburg)

2. Prof. Dr. Gyula Kovacs (FSU Jena)

3. PD Dr. Alexander Rapp (Universitätsklinikum Tübingen)

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Index of Abbreviations

ACC	anterior cingulate cortex
ACh	acetylcholine
ALE	activation-likelihood estimation
AltB	alternation block
AltT	alternation trial
BA	Brodmann area
BOLD	blood oxygenation level dependent contrast
BPRS	Brief Psychiatric Rating Scale
CPZ	chlorpromazine
CNS	central nervous system
CNTRICS	Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia
CNV	copy number variant
DA	dopamine
DLPFC	dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
EMG	electromyography
EMMN	expression related mismatch negativity
ES	expectation suppression
EVC	early visual cortex
ε	prediction error
FEF	frontal eye field
FFA	fusiform face area
FG	fusiform gyrus
FGA	first-generation antipsychotic
fMRI	functional magnetic resonance imaging
fMRIa	functional magnetic resonance imaging adaptation
FWHM	full-width at half maximum

GWAS	genome-wide association study
HC	healthy controls
5-HT	5-hydroxytryptamine (serotonin)
ICD	International Statistical Classification of Diseases and Related Health Problems
IFG	inferior frontal gyrus
IOG	inferior occipital gyrus
IPS	intraparietal sulcus
ISI	inter-stimulus interval
ITI	inter-trial interval
ITG	inferior temporal gyrus
LGN	lateral geniculate nucleus
LO	dorsocaudal part of the lateral occipital complex
LOC	lateral occipital complex
LSD	least significant differences
MEG	magnetoencephalography
MFG	medial frontal gyrus
MMN	mismatch negativity
MNI	Montreal Neurological Institute
MP RAGE	magnetisation prepared rapid gradient echo
MRI	magnetic resonance imaging
MTG	middle temporal gyrus
MTL	medial temporal lobe
OFA	occipital face area
OTC	occipital temporal cortex
PC	predictive coding
PFC	prefrontal cortex
PGC	Psychiatric Genomics Consortium
PPI	prepulse inhibition
p(rep)	repetition probability

PVC	primary visual cortex
RE	repetition enhancement
RepB	repetition block
RepT	repetition trial
ROI	region of interest
RS	repetition suppression
RSI	repetition suppression index
RT	reaction time
SANS	Scale for Assessments for Negative Symptoms
SAPS	Scale for Assessments for Positive Symptoms
SCID	Structural Clinical Interview for DSM Disorders
SFG	superior frontal gyrus
SGA	second-generation antipsychotic
SLF	superior longitudinal fasciculus
SNPs	single-nucleotide polymorphisms
STG	superior temporal gyrus
STS	superior temporal sulcus
SZ	patients with schizophrenia
TMS	transcranial magnetic stimulation
TPJ	temporoparietal junction
VBM	voxel-based morphometry
VFC	ventral frontal cortex
VLPFC	ventrolateral prefrontal cortex
vMMN	visual mismatch negativity
VMPFC	ventromedial prefrontal cortex

Summary

Abnormal processing of faces, a salient and social stimulus class, is a feature of cognitive dysfunction in schizophrenia. The major face processing areas are the fusiform face area (FFA), the occipital face area (OFA) and the dorsal-caudal region of the lateral occipital complex (LO). Hierarchical top-down prediction presumably from prefrontal areas to the occipitotemporal cortex relies on intact regional processing of faces. These feedback connections are thought to be disturbed in schizophrenia due to dorsolateral/medial prefrontal dysfunctions and/or prefronto-temporal disconnection. Recent studies in healthy subjects have suggested feedback connections between prefrontal and face-selective areas to be relevant in repetition probability (p(rep)) paradigms with predictive coding (PC) as underlying neural model. It is unclear, however, at which level of this processing hierarchy deficits in schizophrenia might emerge.

In the present study, we tested hypotheses related to altered face perception in schizophrenia in a p(rep) paradigm. Our hypotheses were threefold: 1) Patients with schizophrenia (SZ) show altered BOLD (blood oxygenation level dependent contrast) responses to neutral faces in occipitotemporal face processing areas (FFA, OFA, LO) compared to healthy controls. 2) SZ show deficits in regional brain activation specific to the repetition suppression (RS) effect. 3) SZ show lower activation related to context modulation on RS as a correlate of impaired prediction.

In order to test these hypotheses, we used functional magnetic resonance imaging (fMRI) at 3 Tesla and a previously studied RS paradigm (Kovacs et al. 2008, Summerfield et al. 2008) in 17 patients with DSM-IV/DSM-5 schizophrenia (in remission from a previous psychotic episode) and 17 healthy controls (HC) matched for age, gender, and education. Pairs of neutral face stimuli were presented in repetition trials (RepT) or alternation trials (AltT), which were arranged in blocks. The likelihood of repetitions within these blocks was either high (75% in repetition blocks (RepB)) or low (25% in alternation block (AltB)), thus testing the modulating impact of p(rep) effects on RS for both groups in a region-of-interest (ROI) analysis of the investigated areas (FFA, OFA and LO). For our analysis, we first tested the overall BOLD response in these ROIs (i.e. activation across both trials, and irrespectively of RepB or AltB). Second, we then assessed the RS effect as the activation difference between AltT and RepT during the RepBs. Third, we analysed context modulation

effects by computing the interaction of TRIAL (AltT, RepT) by BLOCK (AltB, RepB) as an indicator of prediction effects.

The results showed: 1) There was no group difference in overall activation related to neutral faces in the FFA. However, we found a significantly reduced BOLD response of the OFA and LO in SZ, when compared to HC. 2) We found a consistent RS effect on brain activation for both groups in all investigated regions. 3) We found significant interactions of block-trial conditions (i.e. larger RS in RepB compared to AltB) in all areas investigated and not being different between the two groups. In an additional whole-brain analysis of the block-trial condition, we found activation in a network including the bilateral superior temporal gyrus (STG), right transversal temporal gyrus, insula, and parahippocampal gyrus during p(rep) modulation in SZ; as well as left STG and bilateral lingual gyrus in HC.

Our findings emphasise the role of the FFA as a key-region for face processing in schizophrenia, possibly compensating for unspecific response reductions in earlier face processing areas of OFA and LO in SZ. Moreover, the results suggest that RS and thus selectivity to individual face images is preserved in SZ. Considering our findings in the context of abnormal salience processing in schizophrenia, they suggest that associative salience for faces (as value attribution) seems to be intact. The findings show robust local processing of neutral faces in the ventral visual stream in SZ. We did not find evidence that functional deficits affect RS per se. Also, the lack of group difference in p(rep) modulation of RS might be attributed to the mostly intact processing in face-selective regions. Lack of prefrontal task activation (as a putative correlate of top-down deficits) might be related to the experimental conditions and resulting compensation in the p(rep) paradigm. One interpretation is that higher-order cortical predictions are utilised only when experimental conditions demand additional cognitive resources. Hence, p(rep) modulation of RS might be accomplished within the functioning of disturbed cerebral networks in SZ. Higher-level involvements (e.g. of prefrontal areas) might be a dynamic mechanism to further increase efficiency, and switching from ventral to dorsal system might be relevant in the dynamic involvement of prediction areas.

Zusammenfassung

Die gestörte Verarbeitung von Gesichtern, als saliente und soziale Stimuli, ist ein Kernaspekt kognitiver Dysfunktion der Schizophrenie. Die für die Gesichter-Verarbeitung wichtigsten Areale sind das fusiforme (FFA), das okzipitale Gesichtsareal (OFA) und der dorso-kaudale Teil des lateral okzipitalen Komplexes (LO). Die hierarchische „top-down“ Vorhersage von (vermutlich präfrontalen) Arealen, hin zum okzipitotemporalen Kortex basiert auf intakter, regionaler Verarbeitung von Gesichtern. Diese Feedback-Verbindungen scheinen bei Schizophrenie gestört zu sein, basierend auf dorsolateral/medial präfrontalen Aktivierungsdefiziten und/oder gestörter präfrontotemporaler Konnektivität. Studien mit Gesunden teilen diesen Verbindungen in Paradigmen zur Wiederholungswahrscheinlichkeit (p(rep)), im Rahmen von Modellen des prädiktiven Kodierens (PC), eine wichtige Rolle zu. Es war bisher unklar, auf welcher Ebene der hierarchischen Verarbeitung die Defizite bei Schizophrenie auftreten.

In dieser Studie wurden folgende Hypothesen in Bezug auf veränderte Gesichter-Wahrnehmung bei Schizophrenie im p(rep) Paradigma untersucht: 1) Patienten mit Schizophrenie (SZ) zeigen eine veränderte BOLD-Antwort (blood oxygenation level dependent contrast) auf neutrale Gesichter in okzipitotemporalen Arealen (FFA, OFA, LO). 2) SZ weisen Defizite in der wiederholungsbedingten Signalunterdrückung (repetition suppression, RS) auf, einem Charakteristikum regionaler Aktivität der Gesichtsareale. 3) SZ zeigen verminderte Aktivität hinsichtlich einer kontextuellen Modulation von RS als Ausdruck einer gestörten Vorhersage von Wiederholungen.

Um diese Hypothesen zu überprüfen wurde ein zuvor untersuchtes RS-Paradigma (Summerfield et al. 2008, Kovacs et al. 2012) mittels funktioneller Magnetresonanztomographie (fMRT) bei Schizophrenie angewendet. 17 Patienten mit DSM-IV/DSM 5 Schizophrenie (in Remission nach psychotischer Episode) und 17 gesunde Kontrollen (HC), in Geschlecht, Alter und Bildungsabschluss einander zugeordnet, wurden untersucht. Paare von sich wiederholenden (RepT) oder verschiedenen (AltT) neutralen Gesichtern wurden in Blöcken präsentiert, die eine hohe (75% in repetition blocks (RepB)) oder niedrige (25% in alternation blocks (AltB)) p(rep) aufwiesen. So konnte der modulierende Einfluss von p(rep) auf RS für beide Gruppen in einer ROI-Analyse (region-of-interest, ROI) der betrachteten Areale (FFA, OFA und LO) getestet werden. Wir untersuchten zuerst den allgemeinen

BOLD Effekt dieser Areale (d.h. Aktivierung über TRIAL, unabhängig von BLOCK). Dann wurde der RS-Effekt ermittelt, als der Unterschied der Aktivierungen zwischen AltT und RepT während der RepB. Zuletzt wurde der Kontext-modulierende Einfluss mittels einer Interaktion von TRIAL (RepT, AltT) und BLOCK (RepB, AltB) als Indikator eines Vorhersage-Effekts berechnet.

Die Ergebnisse zeigten: 1) keinen Gruppenunterschied in der allgemeinen Aktivierung auf neutrale Gesichter in der FFA, während OFA und LO bei SZ jeweils einen signifikant kleineren BOLD-Effekt aufwiesen als die Kontrollgruppe. 2) RS konnte in allen Arealen für beide Gruppen gezeigt werden. 3) Es konnte eine signifikante Interaktion von BLOCK und TRIAL-Bedingungen gezeigt werden (d.h. RS war in RepB stärker als in AltB), in allen untersuchten Arealen und ohne einen Gruppenunterschied. In der zusätzlich durchgeführten Analyse über das gesamte Gehirn fanden wir die Aktivierung von Netzwerken, welche bilateral superior temporale Areale (STG), den rechten transversalen temporalen Gyrus, die Inselrinde und den parahippokampalen Kortex im p(rep)-Paradigma bei SZ; und den linken STG, sowie bilateral linguale Areale für HC umfasste.

Die Resultate verdeutlichen die Schlüsselrolle des FFA, die möglicherweise die generalisierte, verminderte Antwort von früheren Gesichter-verarbeitenden Arealen, OFA und LO, bei SZ kompensiert. Darüber hinaus zeigten wir, dass RS und somit die Selektivität für individuelle Gesichter bei SZ erhalten ist. Betrachten wir unsere Erkenntnisse im Zusammenhang mit abnormaler Salienz bei SZ, so lassen diese eine intakte, assoziative Salienz (d.h. eine Bedeutungsverknüpfung) zu Gesichtern vermuten. Diese Studie zeigt eine robuste, lokale Verarbeitung neutraler Gesichter im ventralen visuellen System bei SZ. Wir können nicht bestätigen, dass funktionelle Defizite RS, per se, beeinflussen. Auch der fehlende Gruppenunterschied in der p(rep)-Modulation wird einer weitgehend intakten Verarbeitung von Gesichtern in den selektiven Arealen zugeschrieben. Die fehlenden präfrontalen Aktivierungen könnten von experimentellen Bedingungen abhängig sein. Höhere Areale würden somit nur genutzt werden, wenn zusätzliche Ressourcen erforderlich sind. Dann könnte eine Modulation von RS durch p(rep) innerhalb der Kapazitäten des gestörten Netzwerkes kompensiert werden. Eine Beteiligung höherer/präfontaler Areale könnte ein dynamischer Mechanismus zur Effizienz-steigerung sein, relevant dabei der Wechsel vom ventralen zum dorsalen System.

1. Introduction

Alteration in the perception of faces as one of the most salient stimuli leads to social and behavioural deficits in schizophrenia (Marwick and Hall 2008). More importantly, face processing might be related to cognitive deficits in various areas, such as attention, executive function, and visual memory. Face processing represents a useful model to study basic perceptual deficits and higher prediction impairments. Until now, face perception was investigated intensively in relation to emotion recognition (Holt et al. 2006, Li et al. 2010, Habel et al. 2010), whereas general face processing is still broadly discussed (Williams et al. 2004, Holt et al. 2006, Bleich-Cohen et al. 2009). Regarding prediction processing, the knowledge of fronto-temporal alterations (Crossley et al. 2009) and general dysconnectivity (Stephan et al. 2009) in schizophrenia might point at a face processing network impaired in its hierarchical organisation (Rao and Ballard 1999). As an influencing component, expertise to faces that is required for efficient top-down prediction (Grotheer and Kovacs 2016) might be relevant in schizophrenia as well. In this study we investigated general face processing, the RS pointing on face selectivity and salience, and p(rep) modulation of RS as a process of the PC model depending on higher level areas.

1.1. Schizophrenia, a disorder of cognitive dysfunction

The modern diagnostic system of schizophrenia, rooted in its historical concepts, and the underlying neurobiological mechanisms conceptualise the cognitive disorder. The general brain structure and function deficits of schizophrenia have importance with regards to correlates of the cognitive disturbance.

1.1.1. Conceptualisation of the cognitive disorder

Historical assumptions

In 1909, Emil Kraepelin (1856-1926) introduced the unified concept of “dementia praecox” to describe a state of delusion, hallucination and excitement that leads to a decrease in “intellectual capacity” (Jablensky 2007). Swiss psychiatrist Eugen Bleuler

(1857-1939) questioned this model with respect to both the early-onset ("praecox") and the worsening in a serious mental deterioration ("dementia") (Hoff 2012). Instead, he argued in favor of a broader term with more optimism on prognosis, and thus the term schizophrenia was born: "Split mind" describing a loss of associative connections, was seen as the most prominent characteristic of the disease (Bleuler 1950, Hoff 2012). Bleuler presented a division into basic (disorder of association, ambivalence, and autistic behaviour) and accessory symptoms (acoustical hallucinations, paranoia or psychomotor abnormalities, Hoff (2012)). The first rank symptoms, such as passivity phenomena and thought insertions were defined by Kurt Schneider (1887-1967) (Schneider 1959). On a neurobiological level, Bleuler explained the "changing of associations" with a lack of "physiological inhibitions and pathways" (Bleuler 1950). Kraepelin proposed an attribution of cognitive deficits to cerebral localisations in frontal and temporal areas (Andreasen and Olsen 1982). These first approaches have shaped the course of neurobiological investigations of the disorder. The term 'schizophrenia' became a major psychiatric concept, even though both Kraepelin and Bleuler acknowledged its heterogeneity (Hoff 2012).

Modern diagnostic systems

Standardised operational criteria for schizophrenia are defined by the International Statistical Classification of Diseases and Related Health Problems (ICD, currently, 10th version ICD-10) as well as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Table I, American Psychiatric APA (2013a)).

Diagnostic criteria and content according to DSM 5 (* DSM IV)	
A	Characteristic Symptoms: (1) Delusions, (2) Hallucinations, (3) disorganised speech, (4) grossly disorganised and catatonic behaviour, (5) negative symptoms; Two (or more) of the symptoms are present, in a significant time period (1 month) and at least one of these must be (1), (2) or (3); **Only one criterion is required, if: delusions are bizarre, commentary voice hallucinations or hallucination of two or more conversing voices exist*
B	Social/occupational dysfunction: work, interpersonal relations or self-care; functioning disturbance in one or more of the following fields; level is markedly below the prior the onset achieved level

C	Duration: disturbance persists for at least 6 months; including one month of criterion A, e.g. active-phase symptoms; period may include phases of prodromal and residual symptoms, e.g. only negative symptoms or attenuated forms of the criterion A symptoms
D	Schizoaffective and mood disorder exclusion: Schizoaffective, depressive and bipolar disorders have been ruled out: 1) in active phase: no major depressive, manic or mixed episodes or 2) mood episodes are in minority, seen the total periods
E	Substance/General medical condition exclusion: Disturbance is not associated with physiological effect of a substance or other medical conditions
F	Relationship to a Pervasive Developmental Disorder: History of autism disease or a communication disorder; only additional diagnosis of schizophrenia when prominent delusions or hallucinations have been persisting for one month
	Classification of longitudinal course: 1 year after onset of the active phase; "first episode", "multiple episodes" (≥ 2), "status" and "acute episode", "partial or full remission"

Table I: Diagnostic criteria of schizophrenia: DSM 5 and **DSM IV* (APA 2013a, APA 2013b).

Until recently, DSM-IV criteria were most widely used in research settings, as well as clinical settings in North America. The recently introduced DSM-5 criteria differ only slightly from the DSM IV criteria, such as placing less emphasis on Schneiderian first-rank symptoms and the quality of the delusional symptoms (e.g. bizarre or non-bizarre hallucinations, APA (2013b)). Taken together, this operational definition of schizophrenia accounts for a heterogeneous combination of a range of cognitive, behavioural, and emotional dysfunctions with an inter-individual variation, that affects social life (APA 2013a).

Neurobiological aspects contributing to cognitive deficits

Concepts of schizophrenia have focused on three main theories: schizophrenia being a substantially genetic disorder, a neurodevelopmental disorder, and a disorder of dopaminergic imbalance. These neurobiological factors lead in a variable manner to structural and functional alterations of the brain. The characteristic cognitive deficits might contribute to the hypothesised impairments in face processing and prediction, such as attenuated speed of processing, disturbed executive function, decreased attention holding (Fig. I).

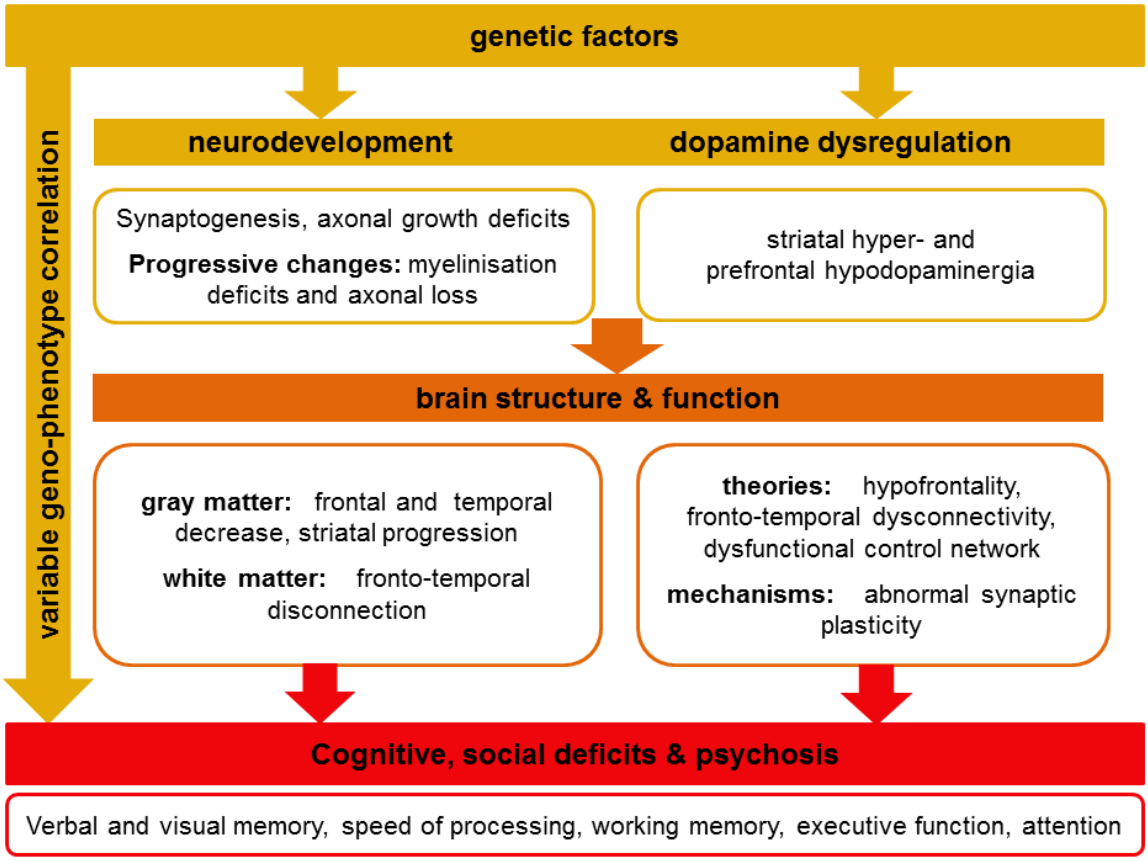

Figure I: The neurobiological concept with focus on genetic factors, neurodevelopmental aspects and the dopamine dysregulation that all contribute to structural and functional alterations in schizophrenia. The sum of all influencing factors lead to cognitive deficits that might heterogeneously contribute to the investigated neuroscientific aspects of face processing in this study.

Historically, classical twin studies have given the first indication of heritability of schizophrenia (Gottesman et al. 1982, Gejman et al. 2011). In 2012, the Psychiatric Genomics Consortium (PGC) estimated that 23% of variation in susceptibility to schizophrenia is captured in single-nucleotide polymorphisms (SNPs) (Lee et al. 2012). PGC 2014 identified genetic risk variation in 128 SNPs, contributing in parallel large (>100kb) and rare (>1%) deletion and duplication of segments of DNA (copy number variants (CNV)) (PGC 2014). Another recent large-scale genome-wide association study revealed SNP networks to be associated with a 70% or greater risk of schizophrenia and underlined the heterogeneity as certain genotypic networks were thought to be responsible for diverse phenotypes (Arnedo et al. 2015). Genome-wide association studies (GWAS) stressed that schizophrenia has a substantial genetic component. Neurodevelopment and dopamine dysregulation both depend on the genetic influence.

Subtle cognitive and social delays in child development have been consistently reported, so that schizophrenia may also be conceptualised as a neurodevelopmental disorder (Pino et al. 2014). Cerebral maldevelopment can be triggered by complications during pregnancy (infections, first or early second trimester events leading to delayed brain growth) and obstetric events (hypoxia, a complex caesarean section, premature labour or Rh incompatibility). Neural correlates of developmental aberrations are abnormal synaptogenesis and axonal growth, depending on reduced protein release during neuronal migration (Pino et al. 2014). In addition to the well-established research on neurodevelopmental pathology, there are also indications of progressive changes after disease onset. While astrogliosis, a classical marker of neurodegenerative diseases, is not present in schizophrenia (Falkai et al. 1999, Harrison 1999), there is evidence that aberrant oligodendrocyte function might underlie myelinisation deficits and axonal loss (Bartzokis et al. 2011, Pino et al. 2014), which might unfold or continue after disease onset.

The dopamine hypothesis included hyperdopaminergic changes in subcortical areas and hypodopaminergia in prefrontal regions (Davis et al. 1991). Recent literature hypotheses claim a “final common pathway” for the genetic, developmental, social and environmental framework of schizophrenia (Howes and Kapur 2009). This multiple-hit hypothesis suggests that several components (fronto-temporal dysfunction, stress, drugs, genes) result in increased dopamine release, followed by aberrant saliency and psychosis proneness (see chapter 1.1.3). Thus, dopamine dysregulation is the most important chemical alteration in schizophrenia. A relationship between the excess release of dopamine from the striatum (i.e. activated dopamine D2 receptor) and the degree of positive psychotic symptoms (Kapur 2003, Howes 2006), as well as the frontal D1 underactivation and working memory/behavioural deficits (Kellendonk et al. 2006) was demonstrated.

1.1.2. General alterations in brain structure and function

The genetic variation, cerebral maldevelopment, and dopamine dysregulation are components in the disease of schizophrenia leading to specific, but heterogeneous alterations in brain structure and function. Focussing on frontal and temporal regions as possible correlates for face perception and prediction, there is ample evidence for

local structural deficits, fronto-temporal disconnection and functional dysconnectivity.

Grey and white matter abnormalities

Voxel-based morphometry (VBM) studies found the main volumetric decreases in local gray matter notably in the bilateral insula/ STG, dorsal and rostral anterior cingulate cortex (ACC)/ medial frontal gyrus (MFG) and the thalamus (Bora et al. 2011). Meta-analyses using activation-likelihood estimation (ALE) found additional reduction in more posterior areas (posterior cingulate cortex, cerebellum, parietal lobe), caudate, hippocampus/amygdala, and multiple frontal regions (Ellison-Wright et al. 2008, Fornito et al. 2009, Glahn et al. 2008). In first-episode patients, significantly greater caudate head volume points to basal ganglia-thalamocortical circuit disruption (caudate head, thalamus, insula, ACC, inferior frontal gyrus (IFG)) that might mediate the executive deficit. In chronic patients there was a progression of gray matter change in the frontal, temporal cortex and insula (Ellison-Wright et al. 2008). There were no treatment effects in frontal regions (Leung et al. 2011). In a recent meta-analysis of neuroanatomical abnormalities in schizophrenia Bora et al. (2011) assessed a correspondence between local gray matter deficits in frontal, thalamic, temporal regions and white matter disconnection from fronto-striatal to temporal areas. White matter was decreased in interhemispheric fibers, anterior thalamic radiation, cingulum, fornix, inferior longitudinal fasciculi and inferior frontal occipital fasciculi. Thus, prior findings of MFG/ACC and MTL white matter decrease were extended (Ellison-Wright and Bullmore 2009). Moreover, the chronic state of the disorder was strongly associated with severe white matter changes (Bora et al. 2011). Importantly, fibers of the corpus callosum between the bilateral dorsolateral prefrontal (DLPFC) were decreased (Wu et al. 2015). But also recent onset and drug-naïve patients showed frontal, fronto-temporal and fronto-limbic connection deficits (Samartzis et al. 2014).

From hypofrontality to network dysfunction

The theory of ‘hypofrontality’ was a popular model for cognitive and social deficits in schizophrenia (Ragland et al. 2007). Historically, it is based on the anterior to posterior gradients of cerebral blood flow found in resting and PET studies (Ingvar and Franzén 1974, Buchsbaum and Wu 1987). Since disrupted prefrontal function was accompanied by temporal/hippocampal functional abnormalities, a hybrid model

of impaired fronto-temporal connectivity was established (Friston et al. 1992). Friston and Frith (1995) showed disrupted functional connectivity reflecting positive symptoms as well as failure to integrate perception (Friston and Frith 1995). Today, the theory of a dysfunctional superordinate control network has been superseded by more sophisticated models. Fronto-temporal connectivity disruption was shown during working memory tasks by Crossley et al. (2009). A meta-analysis across a range of task tapping executive functions has demonstrated a disrupted frontal-based top-down control with core deficits in DLPFC and ACC and has been discussed with regards to a downstream dysfunctional consequence in posterior temporal cortex and mediodorsal thalamus (Minzenberg et al. 2009). In dynamic causal modelling (DCM) analyses, SZ exhibited both ACC-prefrontal-hippocampal hyperconnectivity and ACC-DLPFC/medial-PFC hypo-connectivity (Cui et al. 2015). Resting state findings emphasised thalamocortical dysfunction as a deficit between dorsolateral prefrontal and sensory areas, including visual areas (Klingner et al. 2014). Decreased coupling between left frontal and bilateral subcortical regions, as well as increased coupling between left temporal and bilateral subcortical regions was found in a grey matter analysis (Collin et al. 2013).

Dysconnectivity

Friston (2002) emphasised the functional aspects of disconnection being rather relevant for schizophrenia as a cognitive disorder with abnormal integration ability. The term ‘dysconnectivity’ denotes the observed impairment in adaptational processes in schizophrenia (Stephan et al. 2009). Plasticity of synaptic specialisation, cellular morphology, and cytoarchitectonics is thought to be altered depending on experiences (Friston 2002). Consequently, the above presented disturbed neuronal and molecular mechanisms in schizophrenia play a crucial role, such as N-Methyl-D-aspartate receptor (NMDAR) activations that alter the strength of glutamatergic synapses. Dopamine (DA), acetylcholine (ACh) and serotonin (5-HT) regulate NMDARs activity and therefore modulate synaptic plasticity as the main neural equivalent to dysconnectivity (Lau and Zukin 2007). The above-mentioned pathophysiology of dysconnectivity has also been linked to a limited ability of perceptual prediction, since the interacting systems of processing areas has to be capable of rapid plasticity (Stephan et al. 2009).

1.1.3. Salience misattribution as one major cognitive deficit

Since Kraepelin, “intellectual capacity” has played a major role in schizophrenia (Jablensky 2007). In a recent study, cognitive impairment was proposed as a vulnerability marker for developing schizophrenia, especially psychotic symptoms, and as a prognostic factor (Bora et al. 2014). There is evidence supporting general intellectual deficits (i.e. IQ) to be a neurocognitive correlate rather than specific cognitive deficits (Bora et al. 2014), whereas other studies report on patients performing worse in specific domains, such as verbal memory, speed of processing, working memory, executive function, attention and visual memory (Fatouros-Bergman et al. 2014). These cognitive deficits might be seen as a consequence of the heterogeneous neurobiology of schizophrenia (as presented in Fig. I).

In the sociodevelopmental-cognitive model of Howes and Murray (2014), cognitive schemas are seen as a factor of the circuitry and therefore contributing to an increase of the symptomatology (Fig. II).

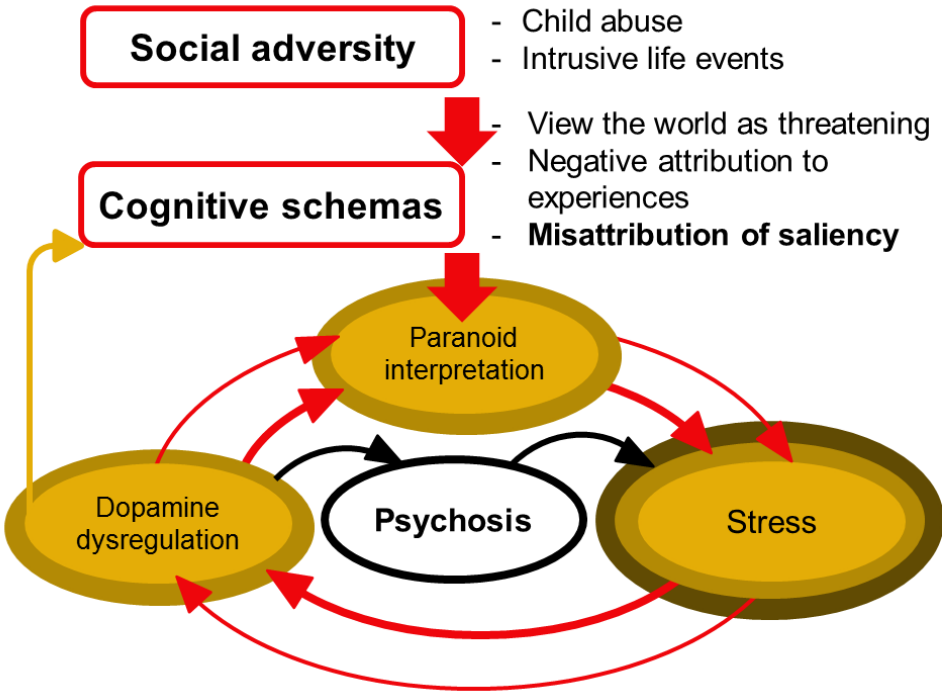

Figure II: The sociodevelopmental-cognitive circuit of schizophrenia. Cognitive schemas that include misattribution of saliency lead to a complex sequence of paranoid interpretations of the environment, stress and increased dopamine dysregulation, and finally to psychosis (see Howes and Murray (2014)).

Experiences of social adversity base cognitive schemas of a threatening, externally

driven and uncontrollable world that leads to misinterpretations of perception. These are postulated to cause paranoid interpretation, under circumstances of genetic and developmental predisposition. The interaction with dopaminergic dysregulation and increased stress triggers misinterpretation of excessive salient stimuli, paranoid interpretations and finally psychosis (Howes and Murray 2014). These insights lead to the need of further neuroscientific evaluation of salience perception in schizophrenia.

1.2. Visual face processing

Face perception is the most developed visual skill in humans (Haxby et al. 2000), but still literature on face processing in schizophrenia shows ambiguous results. RS as an automatic response on face repetitions and the prediction of face repetition are crucial to be tested for schizophrenia. These phenomena allow a characterisation of the face processing network in low-level and top-down processes.

1.2.1. Physiology of face processing

The neural system for face perception is divided in two parts: a) the occipitotemporal core regions of with the inferior occipital gyrus (IOG), the lateral fusiform gyrus (FG), the inferior temporal gyrus (ITG), the superior temporal sulcus (STS) and b) the extended regions of amygdala, limbic, and prefrontal areas (Haxby et al. 2000). Within the core system invariant facial aspects (IOG, FG, ITG) and changeable facial aspects (IOG, STS) are processed (Haxby et al. 2000, Atkinson and Adolphs 2011). In the extended system, social and emotional components are represented (Fairhall and Ishai 2007). As an underlying mechanism, a two-way-directed exchange of information between core and extended regions was proposed (Henson and Rugg 2003, Atkinson and Adolphs 2011).

For the purpose of our study, we focused on the three main face processing regions: the fusiform face area (FFA, Kanwisher et al. (1997)), the occipital face area (OFA, Gauthier et al. (2000)), the dorsocaudal region of the lateral occipital complex (LO,Grill-Spector et al. (1999)). The FFA, located in the fusiform gyrus (FG) is supposed to play the ‘key role’ in the face processing network as it is specialised in

face detection and recognition (Kanwisher and Yovel 2006). The OFA, part of the early visual lateral occipital complex (LOC) (Malach et al. 1995) provides a similar sensitivity to faces (Gauthier et al. 2000). Crucially, it unifies lower-level face versus non-face distinguishing abilities and higher-level shape-extracting, configural/holistic cue-analysis abilities (Atkinson and Adolphs 2011). The LO, activated by object and faces (Malach et al. 1995, Grill-Spector et al. 1999), shows similar adaptation effects as the FFA and the OFA (Kovacs et al. 2012).

1.2.2. Face processing in schizophrenia

The structural abnormalities of face processing regions, such as gray-matter reduction in posterior ITG (Kuroki et al. 2006) and FG (McDonald et al. 2000), might build the fundament for functional deficits, e.g. hypoactivation in right lateral FG. Interestingly, deficits in identity and affect processing were found to be independent from other cognitive deficits as working memory or semantic deficits (Quintana et al. 2003). Also, face-detection and face identity discrimination was found to be impaired (Chen et al. 2009). In contrast to these insights, a recent study reported function and volume of the FFA to be normal (Yoon et al. 2006). Also low-level face discrimination was found to be preserved (Butler et al. 2008). Interestingly, facial emotion processing during working memory tasks showed in a prior study compensation through face movement areas (motor and premotor cortex) in SZ (Quintana et al. 2001).

There is a vast literature investigating facial emotion processing describing a tendency to generalise impaired facial affect processing to neutral face processing disturbance: in relation to STG dysfunction (Williams et al. 2004), hyperactivation in amygdala and hippocampus (Holt et al. 2006) and FFA hypoactivation (Habel et al. 2010). Important to note, aberrant processing of facial emotions was generally related to hypoactivation in the temporal-basal ganglia-prefrontal system (Li et al. 2010). There is no agreement on a primary deficit in face perception as the basis for the misinterpretation of sensory information and perceptional cognitive deficits (Holt et al. 2006, Williams et al. 2004). To differentiate the reduced ability to recognise emotions from an overall face processing disturbance, the adaptation processes after repetition of transfigured-bizarre and natural faces were surprisingly shown to be

equal for both, therefore Bleich-Cohen et al. (2009) concluded a deficit in emotion-related faces. The role of the FG was tested in the “inverted face” paradigm as well, and showed intact face processing. Abnormal processing of facial expression was attributed to reduced co-activation between FG, amygdala and PFC (Bleich-Cohen et al. 2009). Joshua and Rossell (2009) observed a dominance of facial-feature associated encoding methods (i.e. hairstyle or age) and deficits in configural cue-decoding (i.e. relationship between facial features) that impact on social cognitive abilities. This data supported what Frith et al. (1983) had proposed earlier, i.e. schizophrenic patients having difficulties to perceive the integrated “gestalt” of faces.

1.2.3. General neuroscientific aspects of repetition suppression

In this study two neuroscientific aspects of face processing are investigated: 1) The face processing regions are characterised by the RS phenomenon assigning selectivity to individual face images (Desimone 1996). 2) The ability to infer on the occurrence of face repetitions is reflected in the PC as a hierarchical interaction (Rao and Ballard 1999).

Repetition Suppression

RS is one of the most well-known neural phenomena and widely employed in fMRI to characterise functional brain properties. Desimone (1996) observed RS as an intrinsic property of visual areas, important for perceptual learning, and defined it as the experience of a repeated stimulus that attenuates the neuronal response. RS is conceptualised as fMRI adaptation (fMRIa) that describes the haemodynamic attenuation of human BOLD after stimulus repetition (Henson and Rugg 2003). Event-related and local field potentials (Grill-Spector et al. 2006) as well as behavioural studies of habituation describe similar processes (Rankin et al. 2009, Williams et al. 2013). Theoretical models serve to understand the neural mechanisms of RS as a local automatic phenomenon (Fig.III, Grill-Spector et al. (2006)). Fatigue accounts for a response reduction due to an amplitude decline after synaptic depression with reduced neurotransmitter release (Miller and Desimone 1994, Markram and Tsodyks 1996). Sharpening reflects a sparser representation, i.e. a weaker response in the majority of the cells, while most selective cells hold their activity (Desimone 1996, Wiggs and Martin 1998, Gotts et al. 2012). Facilitation

predicts an earlier peak of the fMRI signal due to a synaptic potentiation leading to an acceleration of the information stream (James and Gauthier 2006). However, the computational mechanisms of RS are still discussed: the above-mentioned theories propose a bottom-up flow of sensory information based on relatively automatic encoding. In contrast, more recent models propose top-down cascades of perceptual expectations (Friston 2005, Summerfield et al. 2008).

Predictive Coding

A more complex model is necessary to explain the capacity of the brain to infer on repetitions in term of energetic resources. A hierarchical system encodes incoming stimuli according to their context. The contextual modulation of RS was firstly tested by Summerfield et al. (2008) and showed a reinforcement of RS when face repetitions were more likely. The paradigm was reflected in the PC model according to the neural mechanisms (Rao and Ballard 1999). The objective is the estimation of stable properties of our environment to infer finally on the cause of sensory input (Friston 2005). The single stimulus is not sufficient to interpret the actual state in the outside world and so the brain aims to construct the most rational and plausible interpretation of the sensory data (Feldman and Friston 2010). Therefore, the stream of all perceptual information is continuously decoded to minimise the brain's free energy (Friston 2005, Friston 2010). The mismatch between the expected event, encoded in top-down connections, and the observed event, encoded in the bottom-up connections, is expressed as the prediction error (ε). The continuous recalibration of the higher representation according to the actual sensational input via a feed-forward ε results in more precise feedback prediction of future stimuli and progressively improved identification of stimulus pattern (Fig. III) (Rao and Ballard 1999, Kovacs et al. 2012).

Kovacs et al. (2012) presented significantly larger RS in a condition of more likely repetitions, not only in FFA (Summerfield et al. 2008), but also in the OFA and LO implying expectation effects in those earlier face processing areas. Interestingly, there was lack of a modulation effect for non-face objects and expectation was suggested to depend on the stimulus category (Kovacs et al. 2013). This supports the need of expertise necessary to account for PC model (Grotheer and Kovacs 2016).

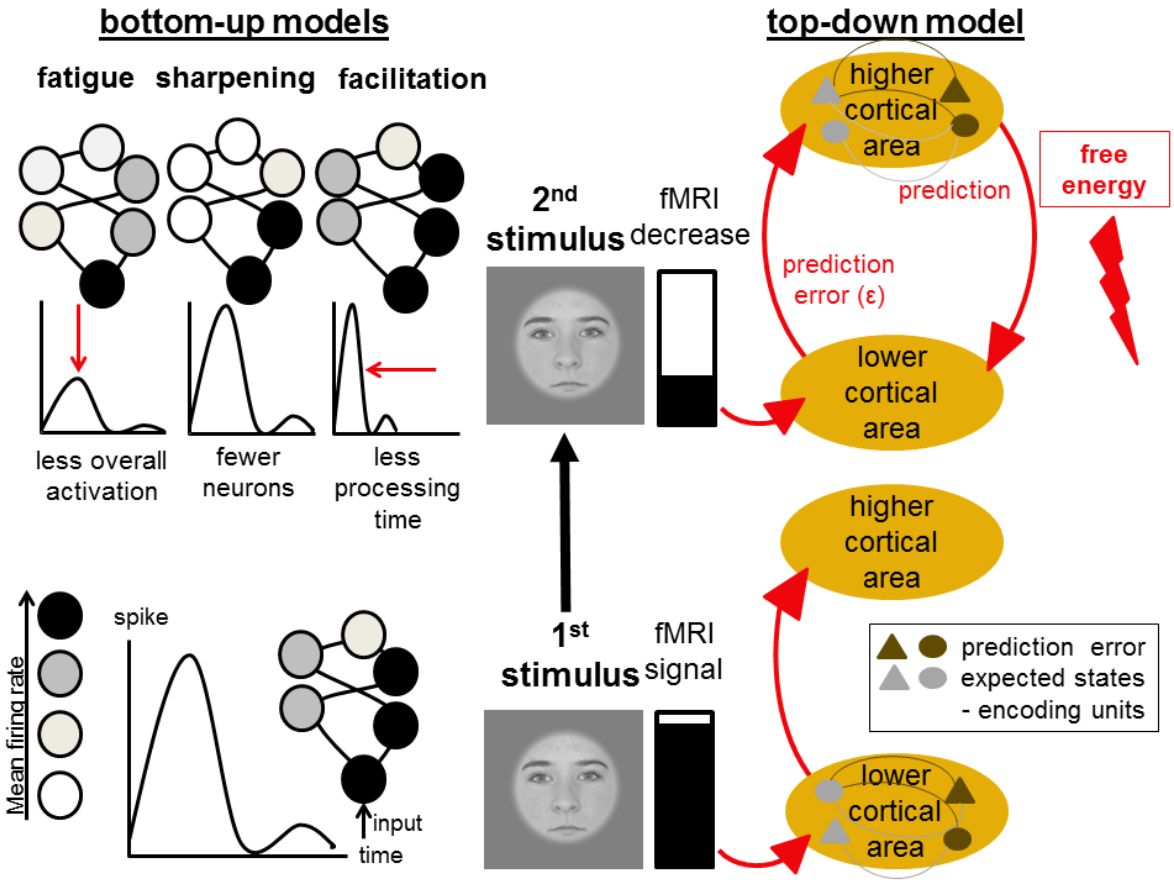

Figure III: Theories of cerebral organisation during RS: the bottom-up model is based on automaticity in representation and the top-down model on hierarchical prediction processing. **Bottom-up models:** the stimulus causes activity (as a function of time) in the neurons (circles coloured accordingly to the mean firing rate). Fatigue - amplitude decrease, sharpening - specialised neurons, facilitation - shortened latency (Grill-Spector et al. (2006), used with permission). **Simplified top-down model**: dynamics on continuous states are explained as a hierarchical exchange of predictions and prediction errors ε, encoded in the neuronal activity of error units and state units on each level. Recognition of repeated stimuli result in additional free energy (adapted from Friston (2010), used with permission).

1.2.4. RS and Predictive Coding in schizophrenia

According to the sociodevelopmental-cognitive circuit hypothesis of schizophrenia, abnormal saliency recognition misleads the cognitive effort to make sense to stimuli (Kapur 2003, Howes and Murray 2014). Salience is a mechanism to capture items in the visual scenery (Santangelo 2015). Face selectivity is a process of salience and thus reflected in the RS occurrence, as well (Wiggs and Martin 1998, Downing et al. 2004). Regarding the neural correlates, both can be understood as automatic processing leading to increased memory strength (Wiggs and Martin 1998, Menon et

al. 2005). In this study, RS is investigated as an adaptation mechanism assigning face selectivity of specialised regions and salience function in schizophrenia.

A large body of mismatch negativity (MMN, Naatanen et al. (1978)) studies, finding attenuated MMN after pattern deviance in SZ, proposes abnormal prediction processing (Baldeweg 2006, Garrido et al. 2009, Wacongne 2016). In light of a corollary discharge study, prediction was assumed to be altered per se (Ford and Mathalon 2012). Crucially, this mechanism to update context with appropriate information is a basis for correct perception (Fletcher and Frith 2009) and failure might provide delusions or more generally, might reflect “propensity for psychosis” (Ford und Mathalon 2012). A theory of abnormal perception connects positive symptoms with the inability to differentiate relevant from irrelevant stimuli (Frith 1979, Fletcher and Frith 2009). Social functioning might be disturbed as well, when distinguishing social cues from the environment fails (Harvey and Lepage 2014). Investigations on prediction are relevant to understand the disease’s influence on those “filter” mechanisms. This study will investigate face perception and prediction in schizophrenia in a paradigm of implicit repetition processing of neutral faces.

2. Aims and Objectives

The analysis of the neural processing of highly salient stimuli such as human face perception is highly relevant to an understanding of disturbed social cognition in schizophrenia. Three hypotheses regarding face perception and prediction in schizophrenia were tested in the light of the studies presented in the introduction:

I.) The first aim was to test the general face processing ability in the face processing areas, FFA (Kanwisher et al. 1997), OFA (Gauthier et al. 2000) and LO (Grill-Spector et al. 1999), that were previously tested in HC. Gray matter volume was found to be reduced in ITG in schizophrenia (Honea et al. 2005, Kuroki et al. 2006) and FG (McDonald et al. 2000). The function of FG was shown to be altered in several studies of emotional and neutral face processing in schizophrenia (Quintana et al. 2003, Williams et al. 2004, Habel et al. 2010), but not all (Quintana et al. 2001, Silverstein et al. 2010).

H1: Neutral face processing is altered in schizophrenia (compared to healthy controls) in FFA, OFA, and LO regions of the face processing ventral stream.

This hypothesis is tested by assessing the response magnitude of the BOLD response in SZ, expected to be significantly different from HC.

II.) The second aim of this study was to evaluate face selectivity in schizophrenia, as measured using the repetition suppression (RS) phenomenon shown in previous studies of healthy subjects (Kanwisher and Yovel 2006, Kovacs et al. 2008, Kovacs et al. 2012). Face selectivity plays a crucial role in attributing salience to stimuli (Downing et al. 2004), and cognitive schemas of salience misattribution are associated with schizophrenia (Kapur 2003, Howes and Murray 2014).

H2: The mechanism of attenuating the BOLD response in face-selective brain areas during repetitions is impaired in schizophrenia as compared to healthy controls.

This hypothesis is tested as the effect of trial, i.e. RS in the face selective areas. We expect a difference between the SZ and HC groups in the RS, with SZ demonstrating a reduced RS effect.

III.) The third aim was to assess impairments in visual prediction processing in schizophrenia. Prior studies in SZ have observed a failure to recognise pattern violations and hypothesised altered mechanisms to update contextual information (Ford and Mathalon 2012, Fletcher and Frith 2009).

The “predictive coding” model (Rao and Ballard 1999, Friston 2005) is the general framework of this study (Kovacs et al. 2012). The environment is encoded more precisely when the correct prediction of the incoming stimulus minimises ε, which in turn is the bottom-up calibrator of top-down predictions. The p(rep) effect on RS is assumed to underlie predictive processes (Summerfield et al. 2008, Kovacs et al. 2012). Therefore, p(rep) modulation of RS was used to assess prediction in schizophrenia. The p(rep) manipulates RS in face processing regions, thus hierarchical regulation of visual prediction can be investigated only indirectly. Prediction of repetitions is thought to be based on prefronto-temporal connections (Summerfield et al. 2008, Kovacs et al. 2012) and therefore to be impaired in schizophrenia. This hypothesis is based on the dysconnection between frontal, thalamic and temporal regions (Bora et al. 2011, Samartzis et al. 2014), studies on prefrontal executive dysfunction (Minzenberg et al. 2009).

H3: P(rep) modulation of RS is altered in schizophrenia, as hierarchical interaction impairments prevent an increased precision of prediction and ε.

This hypothesis is tested as the interaction of block and trial, representing the p(rep) effect on RS. It is expected that SZs do not show this effect, and a group difference is predicted in all of the investigated areas.

3. Methods

3.1. Subjects

We compared 17 patients with DSM-IV / DSM-5 schizophrenia (in remission from a previous psychotic episode) to 17 healthy controls (HC), with groups matched individually for age, gender and education level. All subjects gave written informed consent to the study protocol, which had been approved by the Ethics Committee of the Friedrich Schiller University Jena Medical School, and was in compliance with the Declaration of Helsinki (in its current version).

Inclusion criteria were defined as follows:

a) for the patient group: diagnosis of schizophrenia according to DSM-IV (subsequently confirmed to also meet criteria of DSM-5)

b) for the control group: healthy participants with no current or previous psychiatric disorder or psychiatric / psychotherapeutic treatment, and no first-degree relative with a psychotic disorder.

Exclusion criteria for all subjects were: a major neurological (CNS) or other medical condition (e.g. epilepsy, multiple sclerosis, uncontrolled diabetes or hypertension), learning disability (defined as an estimated (pre-morbid) IQ of <80), a history of traumatic brain injury. Further exclusion criteria for healthy subjects were: use of psychotropic medication (e.g. antipsychotic or antidepressant).

From the initially recruited cohorts, we had to exclude one schizophrenia patient due to technical difficulties during data recording, as well as seven HCs, who either could not be matched to patients of the final SZ sample (n=3) or had a potential history of neurological or psychiatric conditions, which was not revealed at time of study inclusion (n=2), one case due to excessive head movements during the recording (translations of >7 mm, n=1), and one due to impaired task performance raising concerns about validity of data (>50% false positives, n=1).

Regarding the demographical data, the one-by-one matching was made for age (see Table II), gender (13 males per group), and academic achievement expressed by highest school diploma (no group-difference in additional Fisher's exact test p=0.721 (2-sided)). Additionally, IQ was estimated using the multiple choice vocabulary test (Mehrfachwahl-Wortschatz-Test (MWT-B); Lehrl et al. 1995), and handedness was

assessed using the Edinburgh Handedness Inventory (EHI, Oldfield 1971). Groups did not differ in either handedness (Mann-Whitney-U-Test U=120.5; p=0.4; N1=N2=17), IQ (Mann-Whitney-U-Test U=102.0; p=0.1; N1=N2=17). For general information of demographical data see Table II.

Demographical			**SZ**					**HC**		
data	**mean**	**SE**	**SD**	**min**	**max**	**mean**	**SE**	**SD**	**min**	**max**
Age (years)	34.6	2.2	9.0	22	57	34.5	2.1	8.6	25	55
IQ	107.4	3.3	13.8	94	143	103.2	2.7	11.0	92	136
EHI	79.1	6.1	25.1	33.3	100	75.2	7.6	31.3	-20	100

Table II: Demographical data of both groups with mean, SE and range: Age (at time of study) and IQ (multiple choice vocabulary test), handedness (EHI - Edinburgh Handedness Inventory).

Patients were recruited from the in-patient and out-patient services of the Department of Psychiatry and Psychotherapy of Jena University Hospital, and were assessed by a board-certified psychiatrist. All patients met criteria A, B and C for schizophrenia (DSM-IV and DSM-5) with two or more of the characteristic symptoms lasting longer than 6 months and resulting in disturbance of social and occupational functions. Current psychopathology of patients was assessed by the same psychiatrist using the Scale for Assessment of Positive Symptoms (SAPS, Andreasen (1984)) and the Scale for Assessments for Negative Symptoms (SANS, Andreasen (1983)), as well as the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham (1962)). The indicated composite score for negative and positive symptoms is the sum of single item and global item scores of each category i.e. hallucinations, delusion, bizarre behaviour, positive formal thought disorder in SAPS (composite score, range: 0-175) and affective flattening, alogia, avolition-apathy, anhedonia-asociality, attention in SANS (composite score, range: 0-125). Schizophrenia patients were treated with either second-generation antipsychotics monotherapy or polytherapy (SGA, n=13), or a combination of first-generation antipsychotics (FGA) and SGA (n=1), or a combination of SGA and new antipsychotics (n=1); two patients were off antipsychotic treatment (n=2). Chlorpromazine dose equivalents of current antipsychotic medication of patients were calculated following the method developed

by Gardner et al. (2010) and Woods (2003) for second-generation antipsychotics (see Table III). In addition, add-on medication was used for non-psychotic symptoms (see Fig. IV).

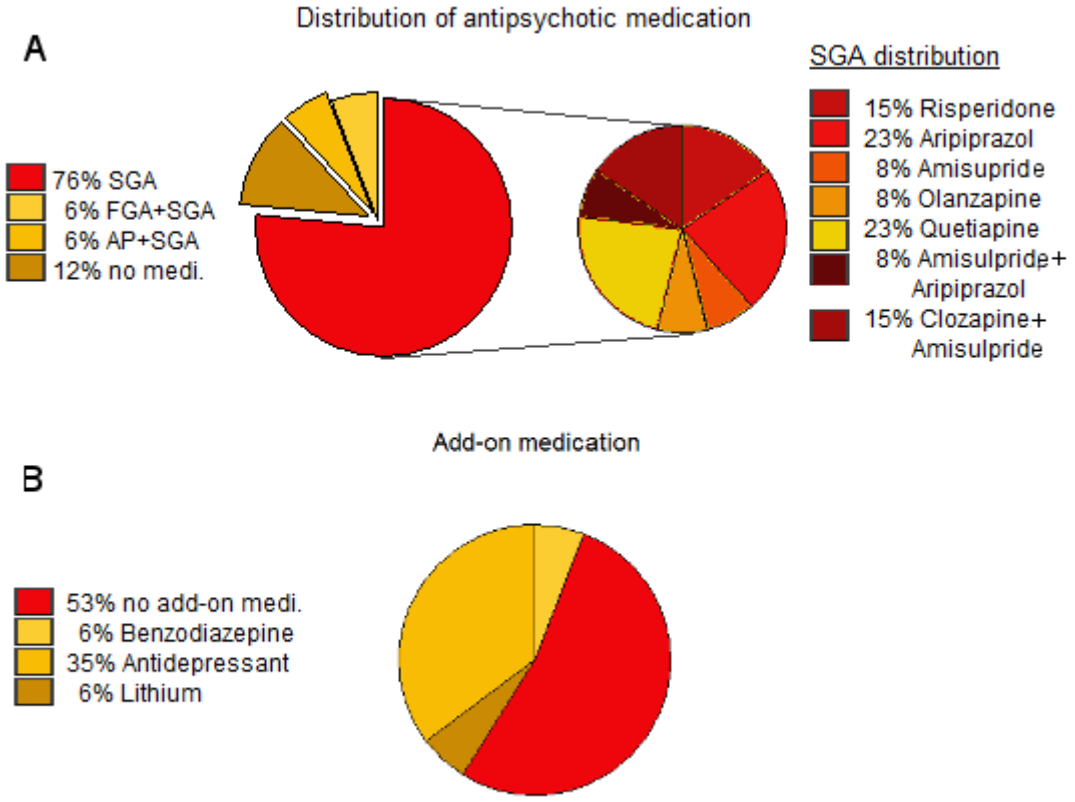

Figure IV: **A)** Distribution of antipsychotic treatment for SZ (N=17): 76% second-generation antipsychotic (SGA), 6% SGA and a first-generation antipsychotic (FGA), 6% with SGA and a new Antipsychotic (AP), 12% without AP medication. For the main group of SGA, the agents are shown in detail. **B)** Add-on medication for non-psychotic symptoms.

Clinical data of SZ	**mean**	**SE**	**SD**	**min**	**max**
SAPS (total / composite score)	13.5	2.3	9.4	1	29
SANS (total / composite score)	36.7	3.9	16.2	7	56
BPRS	34.7	1.8	7.4	22	48
Age of illness onset (years)	25.8	1.6	6.5	18	44
Time since diagnosis (years)	9.4	1.3	5.2	0.5	21
Episodes	2.7	0.4	1.5	1	6
CPZ equivalent (mg/day)	318.7	69.3	268.2	0	997

Table III: Clinical data of SZ (N=17): SAPS and SANS with the composite score (i.e. a sum of the individual score to each item and the category scores) and the BPRS, both evaluate the degree of illness symptomatology at time of study. The age of illness onset in years, the time period since diagnosis and the number of episodes were assessed through interview. Chlorpromazine (CPZ) equivalents were calculated from recent antipsychotic drug medication doses of the subjects.

3.2. Stimulation and procedure

The experimental design was similar to that of a previous study assessing the effect of expectation on repetition suppression in healthy persons (Fig. V; Summerfield et al. (2008), Kovacs et al. (2012), Grotheer et al. (2014)). 240 grey-scale, digital photos of neutral full-frontal Caucasian faces (50% each female and male faces, resp.), similar to the face stimuli used in Grotheer and Kovács (2015) were used. We manipulated the images with GIMP v2.8.2 (GNU Image Manipulation Program). Face images were cropped with a circular mask (diameter=5.5°), luminance and contrast were equalised. For the functional localiser, object stimuli and Fourier randomised versions of these faces and objects were prepared in the same manner. All images were presented in the centre of the screen (height of 2.75° visual angle) on a uniform grey background. Images were back-projected onto a translucent circular screen (diameter, 30°) via a LCD video projector (NEC GT 1150, NEC Deutschland GmbH, Ismaning, Germany, with modified lens for short focal point). The distance of the observer to the screen was 63 cm inside the scanner. The stimulus presentation was controlled via Matlab R2014a (MathWorks), using Psychtoolbox (version 3.0.9).

In the main experiment, we used a mixed design in which single events (i.e. trials) were organised in a frequency-modulating block structure (see Fig. V). Faces were presented pair-wise for 250ms each, separated by an inter-stimulus interval (ISI) that varied between 400 and 600ms and followed randomly by a 1 or 2s long inter-trial interval (ITI). The first stimulus (S1), was either identical to (Repetition Trial, RepT) or different (Alternation Trial, AltT) from the second stimulus (S2). All faces were trial-unique, ensuring that the probability of a repetition per se, and not the frequency of a specific face, was measured. During the ISI and ITI, a fixation cross was presented in the same central location.

In addition to the different trial types, two different types of blocks, consisting of 20 face pairs were presented to the subjects (Fig. V). In the Repetition Blocks (RepB)

75% of the non-target trials were RepT while 25% were AltT. In the Alternation Blocks (AltB) 75% of the non-target trials were AltT and 25% were RepT. RepT and AltT were presented randomly within the blocks. An exception was made for the first four trials of each block, which always consisted of the more frequent trial type of that specific block (RepT in RepB and AltT in AltB). The block structure induced an experimental context of more or less likely repetitions. Thus, four different conditions were presented and analysed in the following order (AltB_AltT, AltB_RepT, RepB_AltT, RepB_RepT). Per run, each block type was presented 4 times. They were shown in an interleaved order, each separated by a 7s-long pause with a centrally shown countdown “Kurze Pause. Nächster Block in…” (Short break. Next block in…).

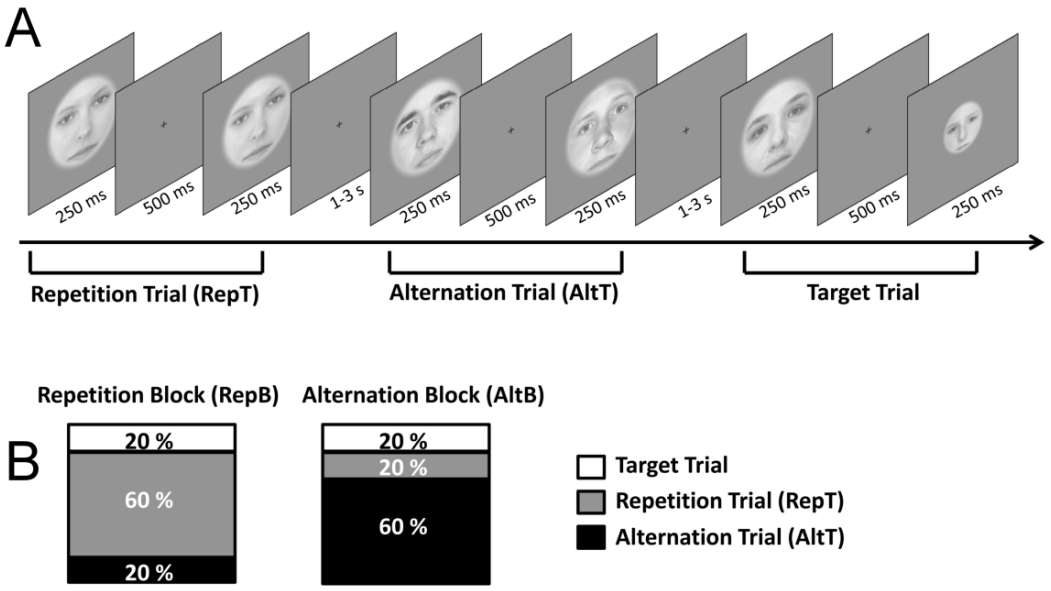

Figure V: The study design with stimulation parameters and arrangements. A) A RepT, an AltT and a target trial are illustrated. Presentation in an interleaved order with a stimulus presentation time of 250 ms, inter-stimulus-interval: 400-600 ms, and inter-trial-interval 1-2s. Standard stimuli: 18% size deviance, target stimuli: 54% size reduction. B) The frequency modulation of trial types within one block-type. In the RepB, the relative probable occurrence of a RepT was 60%, AltT and target trials were presented in 20% likelihood. In the AltB, the AltT were the more probable pairwise stimuli. During a run, RepBs and AltBs were each repeated four times. (Grotheer and Kovacs (2016), used with permission)

Moreover, 20% of all trials were target trials, where target trials could be AltT or RepT with the same relative probability. Hence, size-variations were independent of the block-trial-manipulations (identical to the original work of Summerfield et al. 2008).

The subject's task was to maintain central fixation and to signal the occurrence of the 54% size-deviant face. The stream of standard faces differed by only 18%. Additionally, the size variations reduced local feature adaptation processes in the investigated areas in the brain. The participants were not informed about the trial and block-structure and were asked to answer as quickly as possible. In total, 320 trials were shown. This number of trials was chosen to achieve robust power for analyses, and is higher than in previous studies of repetition suppression for BOLD response in face sensitive areas (shown in the work of Summerfield et al. 2008, Kovacs et al. 2012, Grotheer and Kovacs 2014).

ROIs were determined in a previously obtained functional localiser scan. For this purpose, a simple block-design was used to stimulate the face sensitive areas (FFA, OFA) or face and object sensitive areas (LO), resp., as consistently as possible over a prolonged time period (480s long). Face, object, and Fourier-randomised images of faces were presented in blocks of 40 images during 20s long epochs, interleaved with 20s of blank periods (2 Hz stimulus repetition rate; 300ms exposition time; 200ms of blank). Thus, the stimulus selective activity was maximised.

3.3. Imaging parameters and data analysis

Functional MRI was recorded using a 3 Tesla MR scanner system (Siemens Magnetom Trio, Erlangen, Germany). The functional localiser and the experimental functional scans were successively acquired using a T2* weighted Echo-Planar Imaging (EPI) sequence (34 slices; 10° tilted relative to axial, TR = 2000ms; TE = 30ms; flip angle= 90°; 64×64 matrices; in-plane resolution: 3×3mm; slice thickness 3mm). To obtain a 3D-structural image, high-resolution sagittal T1 weighted images were acquired (magnetisation prepared rapid gradient echo, MP RAGE: TR = 2300 ms; TE = 3.03 ms; 1 mm isotropic voxel size).

Neuroimaging data was pre-processed following a standard approach using SPM8 (Welcome Department of Imaging Neuroscience, London, UK) running under Matlab R2012a (Mathworks, Natick Massachusetts, USA; see Cziraki et al. 2010). The functional localiser and experimental functional scan files were realigned to account for movement based artefacts (Schneider and Fink 2013). Each EPI sequence was spatially matched to the first image of the time series with "rigid-body" transformation

(Friston et al. 1996, Jenkinson et al. 2002). The resulting mean image was co-registered with the anatomical T1 MP-RAGE sequence to reduce distortion susceptibility (Schneider and Fink 2013). All images were normalised to the Montreal Neurological Institute-152 space (MNI) in order to allow for second-level analysis (Schneider and Fink 2013). The images were re-sampled to 2*2*2 mm resolution and smoothed using a Gaussian kernel 8 mm full-width at half maximum (FWHM) (SPM8, Welcome Department of Imaging Neuroscience, London, UK). The aim was to improve the signal-to-noise-ratio (Hopfinger et al. 2000).

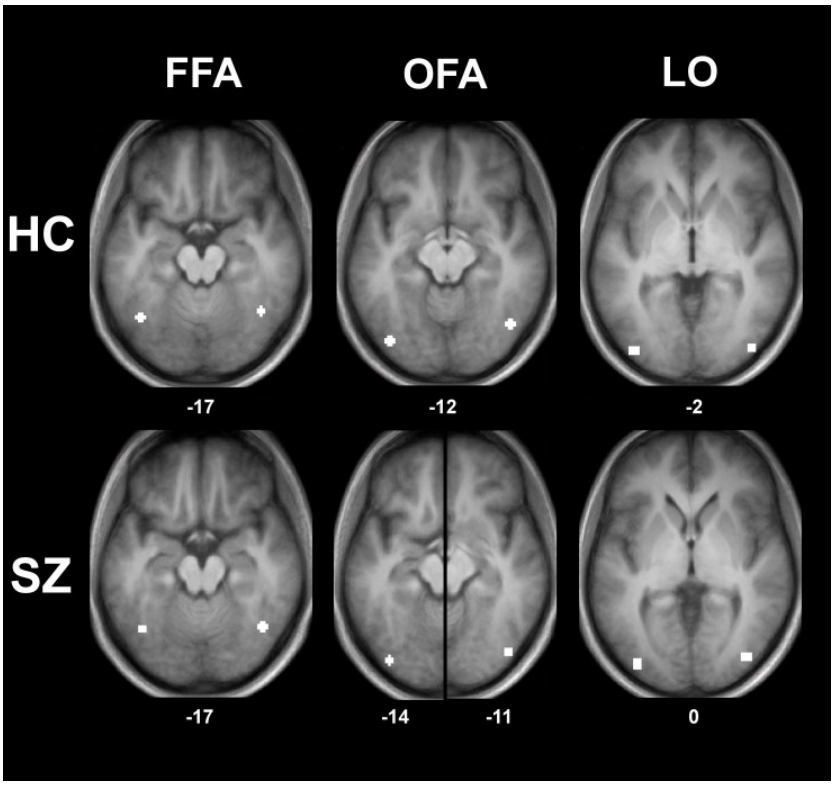

Figure VI: Group results of the functional localiser determined in a first-level analysis, visualised here with spheres on an average brain of each group's participants, showing the significant clusters of ROIs for HC and SZ groups separately. **SZ)** The average MNI coordinates (±SE) of both hemispheres, respectively: FFA [-42 (±1), -64(±2), -18 (±2) and 43(±1), -63 (±3), -17 (±1)], OFA [-40 (±1), -85 (±1), -16 (±1) and 44(±1), -80 (±2), -9 (±1)], LO [-38 (±2), -89 (±2), 1 (±1) and 39 (±2), -84 (±2), 1(±2)]. **HC)** The average MNI coordinates (±SE) of both hemispheres, respectively: FFA [- 43(±1), -63(±3), -17(±1) and 42(±1), -59(±3), -18(±1)], OFA [-41(±1), -81(±2), - 12(±2) and 45(±1), -69(±9), -11(±1)], LO [-40(±1), -88(±1), -2(±2) and 42(±1), -86(±1), -3(±1)].

The first-level analysis was computed using SPM8. ROIs derived from the functional localiser scan were determined on the single subject level using MarsBaR v 0.43

(Brett et al. 2002), by contrasting predictors in a t-test: stronger response to faces than to Fourier-noise and/or to objects ($p<0.001_{UNCORRECTED}$) reflected the FFA [SZ: N=17; average MNI coordinates (±SE): -42 (±1), -64(±2), -18 (±2) and 43(±1), -63 (±3), -17 (±1); HC: N=17; average MNI coordinates (±SE): - 43(±1), -63(±3), -17(±1) and 42(±1), -59(±3), -18(±1); for the left and right hemispheres, respectively] and the OFA [SZ: N=16; average MNI coordinates (±SE): -40 (±1), -85 (±1), -16 (±1) and 44(±1), -80 (±2), -9 (±1); HC: N=16; average MNI coordinates (±SE): -41(±1), -81(±2), -12(±2) and 45(±1), -69(±9), -11(±1) for the left and right hemispheres, respectively]. Stronger response to objects than to Fourier-noise and/or faces ($p<0.001_{UNCORRECTED}$) reflected the LO [SZ: N=17; average MNI coordinates (±SE): -38 (±2), -89 (±2), 1 (±1) and 39 (±2), -84 (±2), 1(±2); HC: N=17; average MNI coordinates (±SE): -40(±1), -88(±1), -2(±2) and 42(±1), -86(±1), -3(±1) for the left and right hemispheres, respectively]. Areas were chosen following anatomical criteria of size and location (Weiner and Grill-Spector 2012) and in accordance to ROI coordinates from former studies (Kovacs et al. 2012). The gaps of ROI identification rather reflects inter-individual variation than relevant difference in the functional architecture (Fairhall and Ishai 2007). The results were visualised using xjView toolbox (Cui 2015). The average locations of these ROIs are presented in Figure VI. ROIs were assessed from significant clusters (spheres in the figure are defined geometric shapes superimposed on co-ordinates).

In order to obtain the percent signal change of our main experiment, we used the canonical Haemodynamic Response Function (HRF) of SPM8 with the four experimental conditions as regressors (AltB_AltT, AltB_RepT, RepB_AltT, RepB_RepT) for a General Linear Models (GLM) analysis of the data. Target trials were modelled as separate regressors, which were not further analysed. We averaged the results of the two runs for each subject and ROI. Then we performed repeated measures ANOVA by using Statistica v. 8.0 (Statsoft, Tulsa, Oklahoma, USA) for each area separately with hemisphere (2 levels), block (2 levels) and trial (2 levels) as within-subject factors and subject group (2 levels: SZ, HC) as between subject factors to determine RS as trial effect and its modulation by p(rep) as block-trial interaction, hemisphere effect respectively. Post-hoc analyses were performed using Fisher's least significant differences (LSD) tests.

To compare the magnitude of repetition suppression in the different blocks for SZ and HC directly, we performed an additional analysis. First, we calculated a repetition suppression index score (RSI) for each block as described previously (Grotheer et al. 2014, Kaliukhovich and Vogels 2011, Axelrod and Yovel 2011) using the equation $RSI=(R_{alt}-R_{rep})/(|R_{alt}|+|R_{rep}|)$, where R_{alt} and R_{rep} were the run-averaged responses in the AltT and RepT within the concerned block. Positive values indicate more pronounced responses in the AltT than in the RepT, negative values indicate the opposite and zero values indicate the absence of any response differences between the two trial types (Kovács et al., 2012). Next, we performed an ANOVA with block (2 levels) as within subject and group (2 levels: SZ, HC) as between subject factor.

The second level analysis was conducted for both the functional localiser and the functional predictive runs of the main experiment. We performed the whole-brain random-effect analyses to test whether our ROI-based approach determined all areas showing a p(rep) modulation effect and whether the groups showed differences in activated brain networks. The data of HC and SZ groups was analysed separately. Contrasts of interest (i.e. face vs. noise, face vs. object, face vs. all, object vs. noise, object vs. all) of the first level analysis were averaged across subjects of each group. The second-level 2x2 repeated measures ANOVA was applied for the two within-subject factors (block, trial) with two levels each (AltB and RepB; AltT and RepT) using SPM 8 (Yang 2012). T-test was conducted for the main effect of block (AltB vs. RepB) and main effect of trial (AltT vs. RepT), F-test for the interaction of block and trial [(AltT_AltB vs. RepT_AltB) vs (AltT_RepB vs. RepT_RepB)]. A averaged structural image for each group was used to visualise the activations in the brain using the commonly applied threshold of $p<0.0001_{UNCORRECTED}$ with a cluster size k >20 voxels using xjView (Cui 2015). Allocation of the coordinates was attributed to regions with Talairach client (Lancaster et al. 2000).

The behavioural data were additionally evaluated by integrating the target trial responses of predictive functional runs in Microsoft Office Excel 2008 and Statistica v.8.0 (Statsoft, Tulsa, Oklahoma, USA) respecting the previously mentioned conditions (AltB_AltT, AltB_RepT, RepB_AltT, RepB_RepT). Repeated measures ANOVA were conducted with run (2), block (2), trial (2) as within-subject factors and group (2, SZ, HC) as between-subject factor for reaction time and hits looking for group differences and main effects.

4. Results

4.1. Performance

On average, the participants needed 889.5ms (SD: ±53.9) to detect the 60% size-deviant face. The groups did not differ in their reaction times (non-significant group effect: $F(1,31)=1.64$, $p=0.21$, $\eta p^2=0.05$). Although no group deviance was found, for explorative reasons groups were compared in their reaction times (Fig. VII-A). The HC group reached an average reaction time of 901.0ms (SD: ±60.4), the SZ group's average was 877.3 ms (44.7 ±SD) with a lack of significant difference in trial condition (non-significant trial effect: $F(1,31)=0.44$, $p=0.51$, $\eta p^2=0.01$). Again, groups did not differ under this condition (non-significant interaction of group and trial $F(1,31)=0.06$, $p=0.81$, $\eta p^2=0.001$). Another condition characterising attention is the block effect that was significantly differing for AltB and RepB (Fig. VII-B, significant block effect: $F(1,31)=4.42$, $p=0.04$, $\eta p^2=0.13$), however, again groups did not differ (non-significant interaction of group and block: $F(1,31)=0.55$, $p=0.47$, $\eta p^2=0.02$). For explorative reasons, the interaction of block and group is presented in Fig. VII-C. Based on our hypothesis, Fisher's post-hoc test was conducted, even if we did not find an interaction between group and block. Only controls showed a significant block difference (Fisher's post-hoc test - SZ: $p=0.35$ and HC: $p=0.05$).

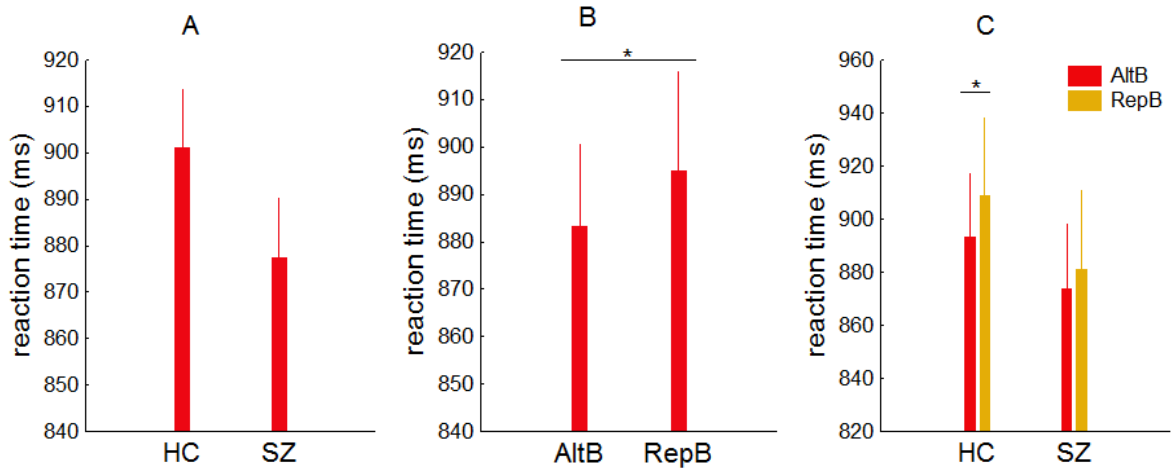

Figure VII: A) Average reaction time in ms (±SE) for target detection in both groups separately, but averaged across runs, blocks and trials. Non-significant group effect. **B)** Average reaction time in ms (±SE) for target detection, separated for condition of block, but averaged across runs, trials and groups. Significant block effect. **C)** Average reaction time in ms (±SE) for target detection in both groups separately and separated for condition of block, but averaged across runs and trials. Non-significant interaction of group and block. Explorative analyses: significant difference of block only in HC. +p ≤ 0.09, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test).

The main effect of run was present for the reaction time, as well (Fig. VIII-A, significant run effect: $F(1,31)=11.64$, $p=0.002$, $\eta p^2=0.27$) and in both groups similarly (non-significant interaction of group and run: $F(1,31)=0.04$, $p=0.88$, $\eta p^2=0.001$). Even if no interaction was found and consequently post-hoc tests were not justified, explorative Fisher's post-hoc test was conducted to differentiate the tendency of attention decrease seen in reaction time decrease between groups (Fig. VIII-B). Both groups showed a tendency of reaction time increase between the runs (Fisher's post-hoc test - SZ: $p=0.03$ and in HC: $p=0.01$).

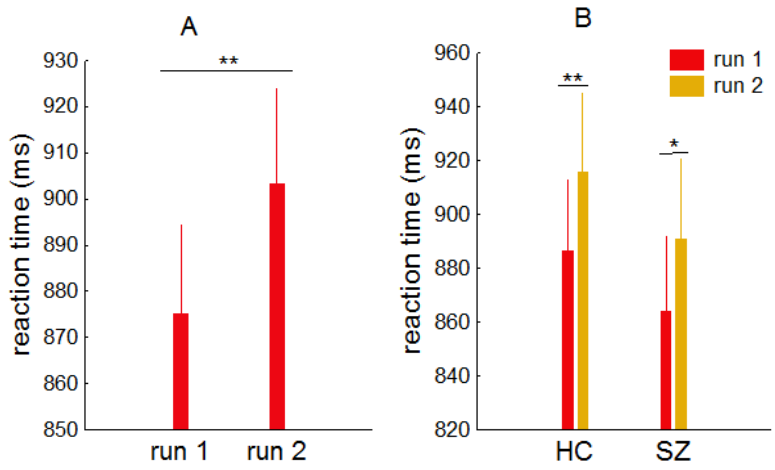

Figure VIII: A) Average reaction time in ms (±SE) for target detection, separated for condition of run, but averaged across blocks, trials and groups. Significant run effect. **B)** Average reaction time in ms (±SE) for target detection in both groups separately and separated for both runs, but averaged across blocks and trials. Non-significant interaction of group and run. Explorative analyses: significant run effect in both groups. +p ≤ 0.09, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test).

The subjects detected the target stimuli on average with 94.4% (SD: ±5.8) accuracy, in the HC group accuracy was at 92.0% (SD: ±7.0) and 96.3% in the SZ group (SD: ±3.3). This tendency of a more correct performance of the SZ group was seen in the group comparison, as well (Fig. IX-A, marginal significant group effect: $F(1,31)=3.73$, $p=0.06$, $\eta p^2=0.11$). None of the groups showed an effect of trial (non-significant trial effect: $F(1,31)=0.30$, $p=0.59$, $\eta p^2=0.01$) and the accuracy in detection of different trials did not depend on groups (non-significant interaction of group and trial: $F(1,31)=0.11$, $p=0.74$, $\eta p^2=0.004$). Further, we found no influence of block on the accuracy in detecting target stimuli (Fig. IX-B, non-significant block effect: $F(1,31)=0.36$, $p=0..56$, $\eta p^2=0.01$), for both groups similarly (Fig. IX-C, non-significant interaction of group and block: $F(1,31)=1.57$, $p=0.22$, $\eta p^2=0.05$). Correct button

pressing was not influenced by fatigue effects (Fig. X-A, non-significant run effect: $F(1,31)=1.15$, $p=0.29$, $\eta p^2=0.04$), and similarly in both groups (Fig. X-B, non-significant interaction of group and run: $F(1,31)=0.65$, $p=0.43$, $\eta p^2=0.02$).

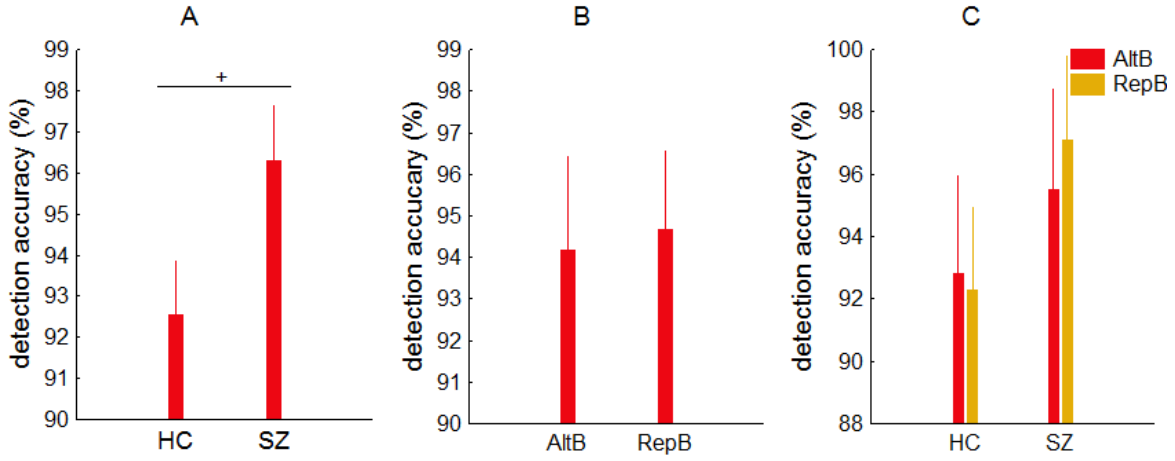

Figure IX: A) Detection accuracy of the correct target stimuli in percent (±SE) in both groups separately, but averaged across run, block and trial. Marginal significant group effect. +p ≤ 0.09, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. **B)** Detection accuracy of the correct target stimuli in percent (±SE), separated for condition of block, but averaged across runs, trials, and groups. Non-significant block effect. **C)** Detection accuracy of the correct target stimuli in percent (±SE) in both groups separately and separated for condition of block, but averaged across runs and trials. Non-significant interaction of group and block. +p ≤ 0.09, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test).

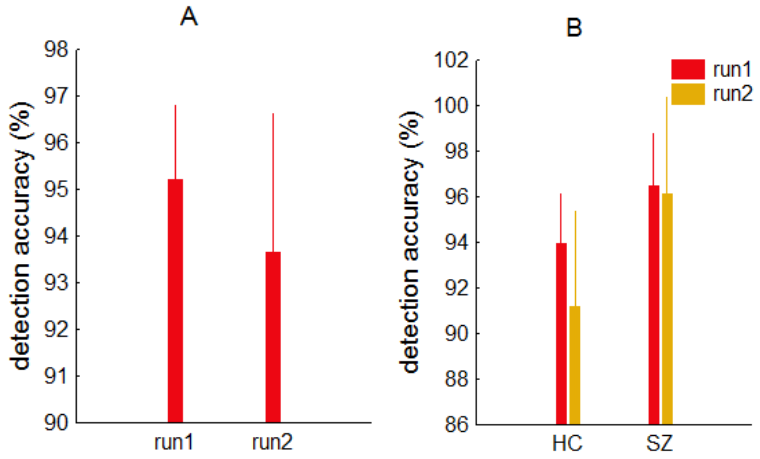

Figure X: A) Detection accuracy of the correct target stimuli in percent (±SE) separated for condition of run, but averaged across blocks, trials and groups. Non-significant run effect. **B)** Detection accuracy of the correct target stimuli in percent (±SE) in both groups separately and separated for both runs, but averaged across blocks and trials. Non-significant interaction of group and run. +p ≤ 0.09, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test).

4.2. Fusiform Face Area

Response magnitude & repetition suppression

In the FFA, the magnitude of the BOLD response representing the local neural activation during face processing was equally large in SZ and HC (non-significant main effect of group: $F(1,30)=1.59$, $p=0.21$, $\eta p^2=0.05$). In Fig. XI-A average peak activation is presented for both groups separately as the hypothesis claimed a significant difference of both groups. Moreover, we observed the expected RS effect only as a tendency of differing strength of response for alternating and repeating pair-wise stimuli similarly for both groups (Fig. XI-B, marginal significant main effect of trial: $F(1,30)=3.18$, $p=0.08$, $\eta p^2=0.1$; Fig. XI-C, non-significant interaction of group-trial: $F(1,30)=0.82$, $p=0.37$, $\eta p^2=0.03$). The trial effect could not clearly be shown in these analyses, for RS in FFA see hereafter the calculation of RS effect in RepB, only.

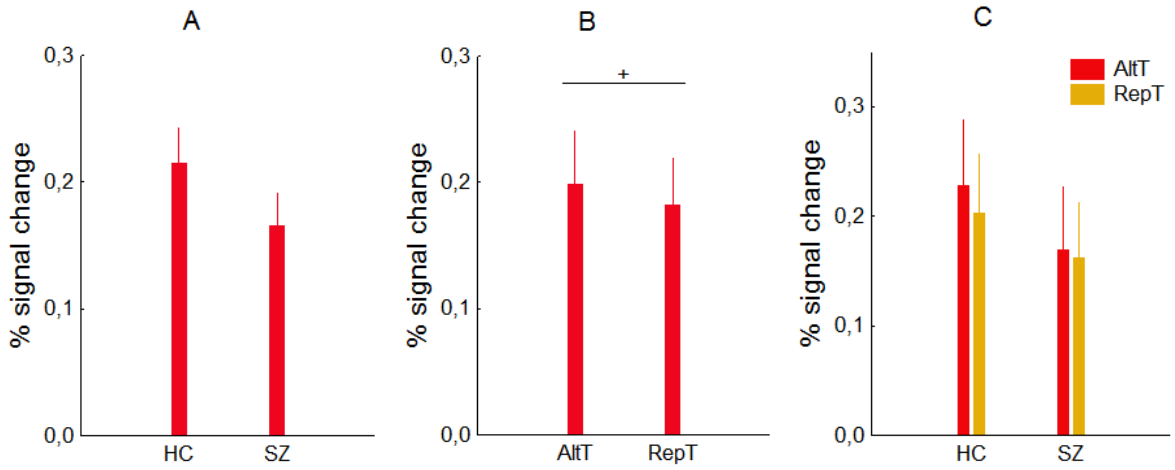

Figure XI: A) Average peak activation profiles (±SE) of the FFA for both groups separately, but averaged across hemispheres, blocks and trials. Non-significant group effect. **B)** Average peak activation profiles (±SE) of the FFA for both trial types separately, but averaged across groups, hemispheres and blocks. Marginal significant trial effect. +p ≤ 0.09 **C)** Average peak activation profiles (±SE) of the FFA for both groups and trial types separately, but averaged across hemispheres and blocks. Non-significant interaction of group and trial.

The BOLD response was larger over the right than over the left hemisphere in both groups similarly (Fig. XII-A, significant main effect of hemisphere: $F(1,30)=4.26$, $p=0.05$, $\eta p^2=0.13$; Fig. XII-B, non-significant interaction of hemisphere-group: $F(1,30)=0.17$, $p=0.69$, $\eta p^2=0.005$). The more detailed view showed that also the response attenuation due to face-repetition, i.e. RS, was larger over the right than

over the left hemisphere, similarly in both groups (Fig. XII-C; significant interaction of hemisphere-trial: F(1,30)=9.1, p=0.005, ηp²=0.23; Fisher's post-hoc test - right: p=0.0003, left: p=0.88; non-significant interaction of hemisphere-trial-group: F(1,30)=0.38, p=0.54, ηp²=0.01). Altogether, these results suggest similar neural processing of faces in the FFA for both groups similarly because of missing interaction effects with the group type.

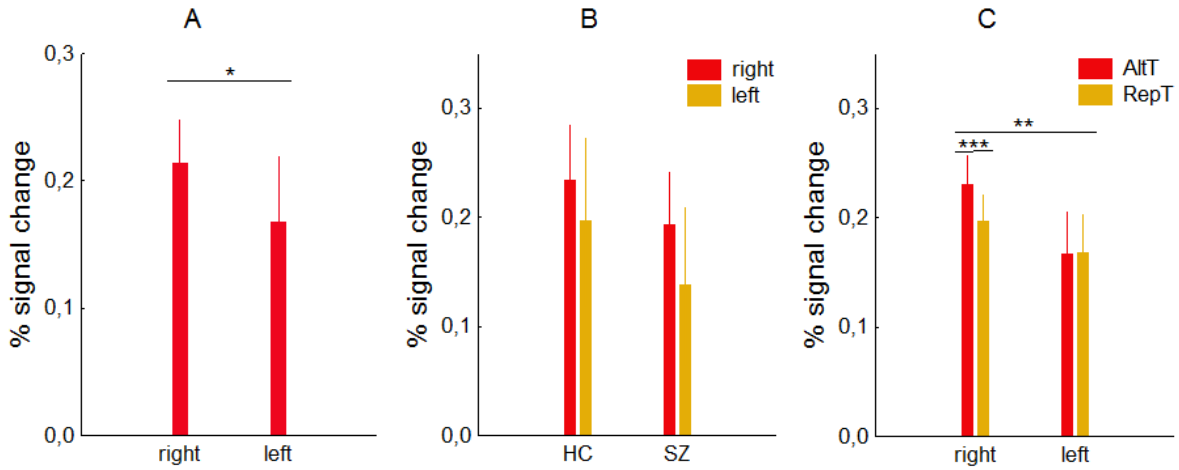

Figure XII: A) Average peak activation profiles (±SE) of the FFA for the hemispheres separately, but averaged across groups, trials and blocks. Significant hemisphere effect. , *p ≤ 0.05 **B)** Average peak activation profiles (±SE) of the FFA for both groups and hemispheres separately, but averaged across trials and blocks. Non-significant interaction of group and hemisphere. **C)** Average peak activation profiles (±SE) of the FFA for the hemispheres and trials separately, but averaged across groups and blocks. Significant interaction of hemispheres and trials. **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test).

Repetition probability modulation

Crucially, the modulation of RS by p(rep) in the alternating and repeating blocks was significant (Fig. XIII-A, significant interaction of block-trial: F(1,30)=19.98, p=0.0001, ηp²=0.4; Fisher's post-hoc test - RepB: p=0.0001 and AltB: p=0.06). Fisher's post-hoc test indicated that the signal suppression was larger in condition of more frequent repetitions than compared to less probable repetitions in AltB. The contradictory course of repetition effect in the different blocks was seen in this analysis. The RS effect was observed in the RepB only and there was a tendency of repetition enhancement (RE) for all subjects. Interestingly, both groups showed a similar robust repetition frequency modulation (Fig. XIII-B; non-significant interaction of block-trial-group: F(1,30)=0.08, p=0.78, ηp²=0.003). For explorative reasons based on the research hypothesis, the interactions of block and trial were indicated for each

group separately (Fisher's post-hoc test to indicate RS in RepB in each group; in HC – AltB: p=0.32, RepB: p=0.001 and in SZ – AltB: p=0.10, RepB: p=0.01; significant interaction of block-trial in groups separately - SZ: $F(1,16)=12.6$, $p=0.002$, $\eta p^2=0.44$ and in HC: $F(1,14)=8.21$, $p=0.01$, $\eta p^2=0.37$).

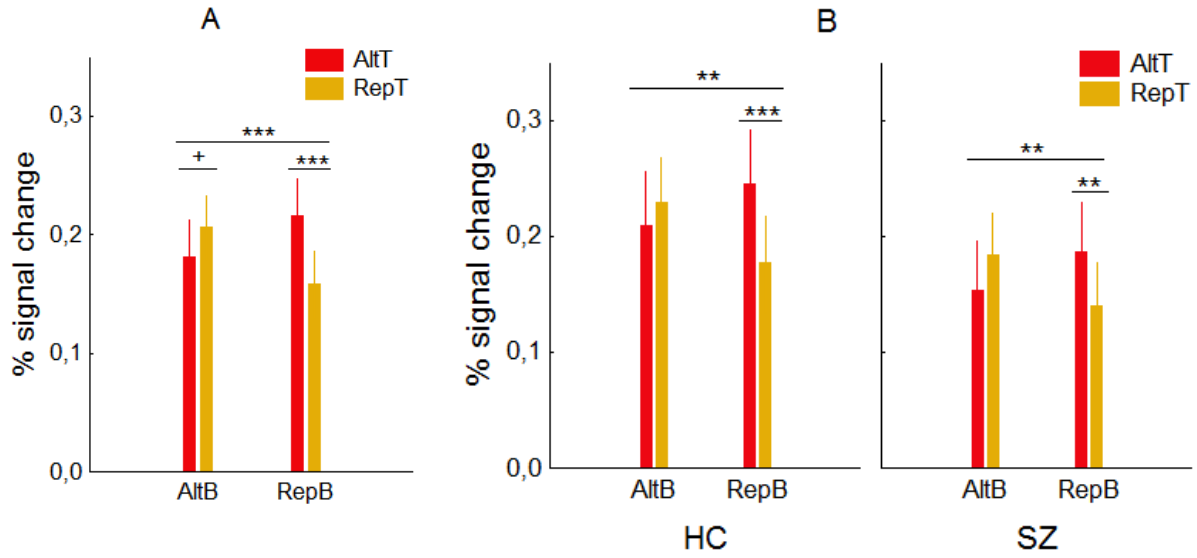

Figure XIII: A) Average peak activation profiles (±SE) of the FFA for the AltTs and RepTs separately for each block, but averaged across groups and hemispheres. Significant interaction of block and trial. Significant RS in RepB and a tendency of RE in AltB. +p≤0.09, ***p ≤ 0.001 (Fisher's post-hoc test) **B)** Average peak activation profiles (±SE) of the FFA for the AltTs and RepTs separately for each block and in dependency to the groups, but averaged across hemispheres. Non-significant interaction of block, trial and group. Explorative analyses: significant interaction of block and trial and significant RS in RepB in both groups. **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test, separate analysis of groups for interaction effects)

Our results indicate a similar processing of repeated face stimuli by a modulation of RS via p(rep) in both groups in the FFA. This was confirmed in the comparison of the RSI. The RSI was larger over the RepB as compared to the AltB (Fig. XIV-A; significant block effect on RSI: $F(1,30)=16.1$, $p=0.0004$, $\eta p^2=0.35$). Both groups presented positive values, i.e. a more pronounced response in RepT compared to AltT, in the RepB only and negative values in the AltB, i.e. the contradictory course with less pronounced response in AltT than in RepT. These results support further the conclusion of similar processing of RS and its modulation by p(rep) in the group of SZ and HC. The RSI did not differ between groups (non-significant main effect of group on RSI: $F(1,30)=0.46$, $p=0.50$, $\eta p^2=0.02$) and again no dependency between groups on block types (Fig. XIV-B, non-significant interaction of block-group on RSI: $F(1,30)=0.13$, $p=0.73$, $\eta p^2=0.004$).

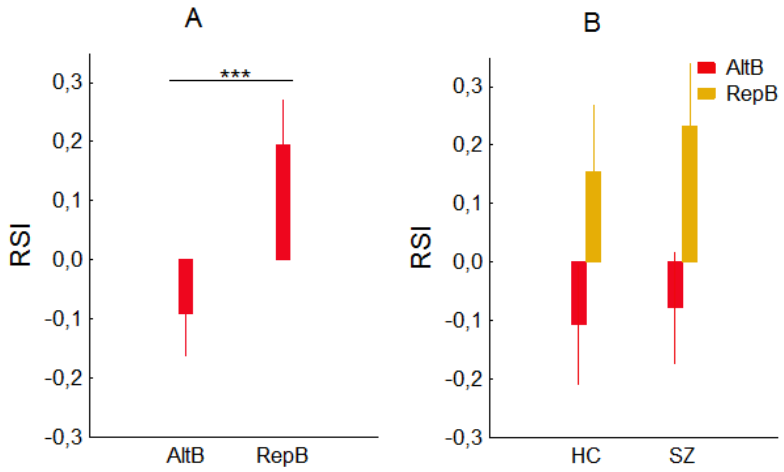

Figure XIV: A) The RSI of the FFA for AltB and RepB separately, but averaged across groups and hemispheres. Significant block effect. Strong modulation of RS by p(rep) in the blocks in both groups. ***p ≤ 0.001 **B)** The RSI of the FFA for AltB and RepB in both groups separately, but averaged across hemispheres. Non-significant interaction of group and block. Positive values indicate more pronounced responses in the AltT than in the RepT, negative values indicate the opposite (Kovács et al., 2012).

4.3. Occipital Face Area

Response magnitude & repetition suppression

In the OFA, the magnitude of the BOLD response was observed to be differing in both groups. There was higher neural activity in the controls than in the patients (Fig. XV-A, significant group effect: $F(1,30)=4.96$, $p=0.03$, $\eta p^2=0.14$). Regarding RS, the effect could not be shown by comparison of response in the trials only (Fig. XV-B, non-significant main effect of trial: $F(1,30)=1.63$, $p=0.20$, $\eta p^2=0.05$). The influence of block-type on the trials was too large. The suppression of RepT in condition of high frequent repetitions (RepB) must be seen apart to conclude on the RS effect in OFA (see below). More importantly, this effect was similar in both groups (Fig. XV-C, non-significant interaction of group-trial: $F(1,30)=0.61$, $p=0.44$, $\eta p^2=0.02$). Similarly to the FFA, we observed a lateralisation of higher response magnitude to the right hemisphere (Fig. XVI-A, significant hemisphere effect: $F(1,30)=15.67$, $p=0.0004$, $\eta p^2=0.34$), but the lateralisation effect is depending on the group type (Fig. XVI-B, significant interaction of hemisphere-group: $F(1,30)=5.83$, $p=0.02$, $\eta p^2=0.16$). The response signal of the OFA was similarly large over both hemispheres in SZ whereas in the HCs the BOLD response was higher over the right compared to the left cortex (Fig. XVI-B, Fisher's post-hoc test - in SZ: $p=0.28$, but significant in HC: $p=0.0001$).

Furthermore, we found a difference in groups looking at the trial effect in both hemispheres (Fig. XVI-C, significant interaction of trial, hemisphere and group: $F(1,30)=4.33$, $p=0.05$, $\eta p^2=0.13$). The response magnitude was significantly larger over the control group. Additionally, the RS effect was shown only over the left hemisphere in the HC group, while SZ showed no difference in the trial-types in both hemispheres (Fisher's post-hoc test in SZ – right: $p=0.22$, left: $p=0.96$; in HC – right: $p=0.19$ and left: $p=0.0005$, non-significant interaction of hemisphere-trial in SZ: $F(1,15)=0.75$, $p=0.4$, $\eta p^2=0.05$; significant in HC $F(1,15)=4.56$, $p=0.05$, $\eta p^2=0.23$).

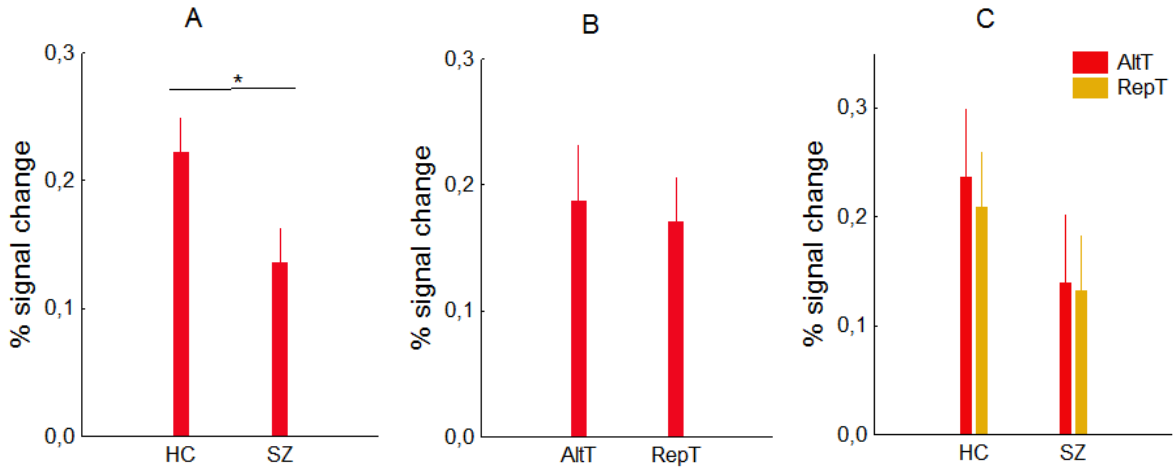

Figure XV: A) Average peak activation profiles (±SE) of the OFA in both groups separately, but averaged across hemispheres. Significant group effect. *p ≤ 0.05. **B)** Average peak activation profiles (±SE) in the OFA for both trial types separately, but averaged across groups, hemispheres and blocks. Non-significant trial effect. **C)** Average peak activation profiles (±SE) of the BOLD response magnitude in the OFA for both groups and trial types separately, but averaged across hemispheres and blocks. Non-significant interaction of group and trial.

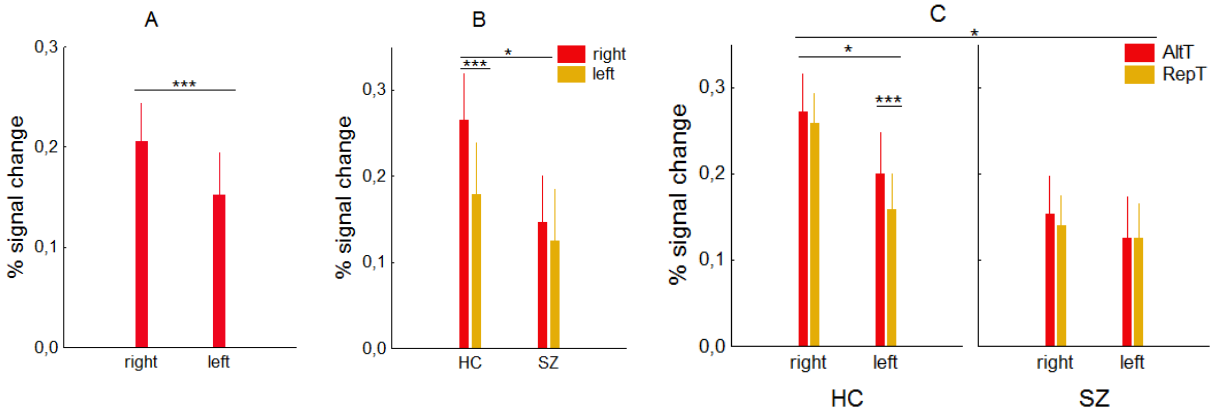

Figure XVI: A) Average peak activation profiles (±SE) of the OFA for the left and the right hemisphere separately, but averaged across groups, trials and blocks. Significant hemisphere effect. ***p ≤ 0.001. **B)** Average peak activation profiles (±SE) of the OFA for the left and the right hemisphere separately for both groups, but averaged across trials and blocks. Significant interaction of hemisphere and group. Significant hemisphere effect only in HC. *p ≤ 0.05, ***p ≤ 0.001 (Fisher's post-hoc test). **C)** Average peak activation profiles (±SE) of the OFA for the AltTs and RepTs for each hemisphere and group. Significant

interaction of hemisphere, trial and group. Significant RS only on the left hemisphere in HC, Non-significant trial-difference for both hemispheres in SZ. *p ≤ 0.05, ***p ≤ 0.001 (Fisher's post-hoc test and interaction effects for HC and SZ in separate analyses).

Repetition probability modulation

As in the FFA, the RS effect was strongly dependent on the p(rep) in OFA, as well. (Fig. XVII-A, significant interaction of block-trial: $F(1,30)=21.04$, $p=0.00007$, $\eta p^2=0.41$, Fisher's post-hoc test, in AltB: p= 0.02, in RepB: p=0.0003). The modulation effect of p(rep) on RS was seen as a significant signal reduction in condition of high frequent repetitions only (RepB), for high frequent alternating trials there was a contradictory course of response modulation, a significant RE. The observed effect was shown similarly in SZ and HC (Fig. XVII-B, non-significant interaction of block-trial-group: $F(1,30)=0.46$, $p=0.5$, $\eta p^2=0.01$; explorative analyses to assess RS in groups separately - Fisher's post-hoc test, in SZ - AltB: p=0.10, RepB: p=0.04 and in HC – AltB: p=0.11, RepB: p=0.001; significant interaction of block-trial in groups separately, SZ: $F(1,15)=10.7$, $p=0.005$, $\eta p^2=0.4$ and in HC: $F(1,15)=10.8$, $p=0.005$, $\eta p^2=0.4$). We conclude a strong influence of block type on RS. Hereby, the missing main-effect of trial for the OFA can be reflected as a subtracting effect of the contradictory course in AltB and RepB. The results of the OFA indicated similar processing of p(rep) dependencies on RS in subjects of schizophrenia and controls.

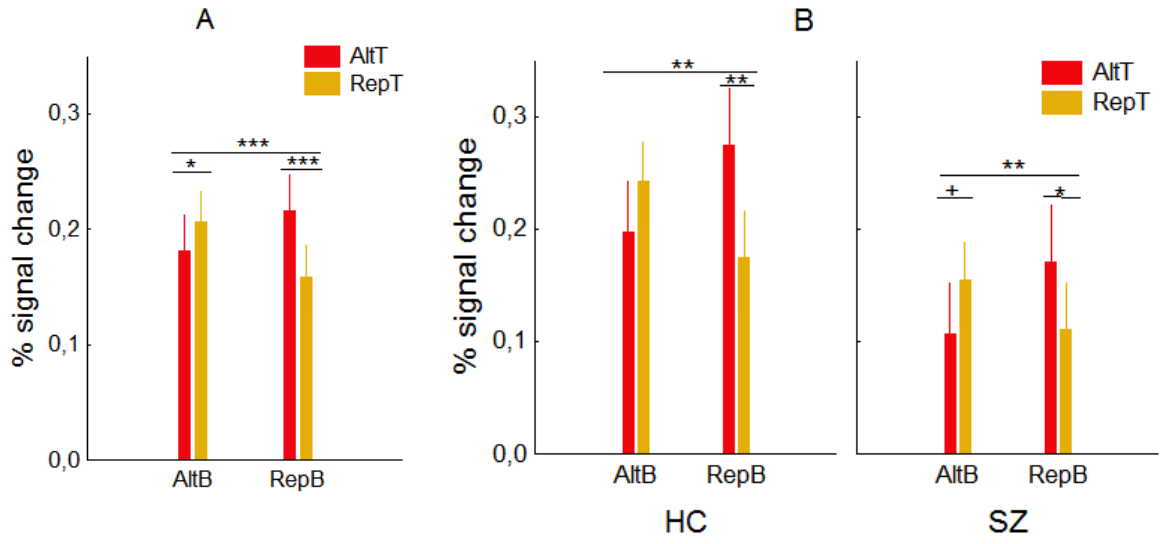

Figure XVII: A) Average peak activation profiles (±SE) of the OFA for the AltTs and RepTs separately for each block, but averaged across groups and hemispheres. Significant interaction of block and trial. Significant RS in RepB and RE in AltB. ***p ≤ 0.001 (Fisher's post-hoc test). **B)** Average peak activation profiles (±SE) of the OFA for the AltTs and RepTs separately for each block and in dependency to the groups, but averaged across

hemispheres. Non-significant interaction of block-trial-group. Explorative analyses: significant interaction of block and trial and RS in RepB in each group separately. **p ≤ 0.01, (Fisher's post-hoc test and interaction effect for HC and SZ in separate analyses).

In accordance with the previous analysis, the analysis of RSI indicated RS in the RepB with positive values, but in the AltB only negative values (Fig. XVIII-A, significant block-effect: $F(1,30)=17.10$, $p=0.0003$, $\eta p^2=0.36$). Groups did not differ concerning the block-type influence on RSI (Fig. XVIII-B, non-significant interaction of block and group: $F(1,30)=0.03$, $p=0.87$, $\eta p^2=0.0009$). The results confirmed above mentioned similarity of groups regarding the p(rep) modulation effect (non-significant group effect on RSI: $F(1,30)=0.07$, $p=0.80$, $\eta p^2=0.002$). Insofar groups differ in the response magnitude in the OFA, but not in the modulating pattern of p(rep) on the RS effect itself.

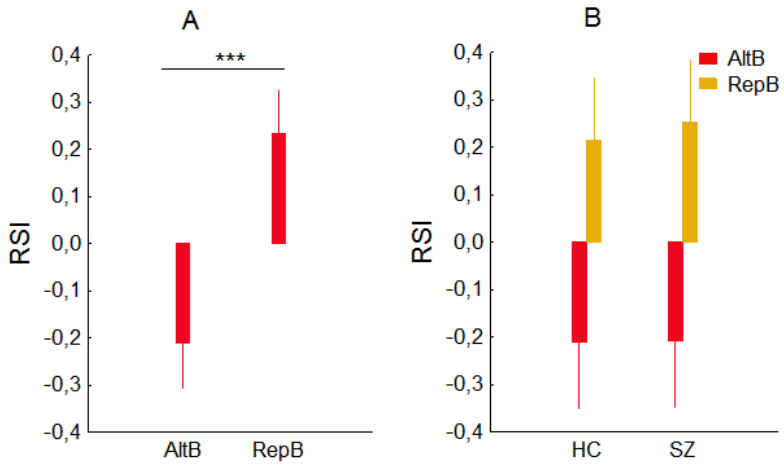

Figure XVIII: A) The RSI of the OFA for AltB and RepB separately, but averaged across groups and hemispheres. Significant block effect. Strong modulation of RS by p(rep) in the blocks in both groups. ***p ≤ 0.001. **B)** The RSI of the OFA for AltB and RepB in both groups separately, but averaged across hemispheres. Non-significant interaction of block-group. Positive values indicate more pronounced responses in the AltT than in the RepT, negative values indicate the opposite (Kovács et al., 2012).

4.4. Lateral Occipital Area

Response magnitude & repetition suppression

LO showed a strong group difference since there was a strongly attenuated magnitude of the BOLD signal in SZ, even larger than in OFA (Fig. XIX-A), with a significant main-effect of group: $F(1,32)=9.49$, $p=0.004$, $\eta p^2=0.23$). In accordance to the OFA, there was missing suppression of the signal when faces repeated in the LO, as well (Fig. XIX-B, non-significant main-effect of trial: $F(1,32)=1.77$, $p=0.2$, $\eta p^2=0.05$). The influence of block-types on trial effects are evaluated as follows: Groups did not differ in their response dynamics on repeating or alternating stimuli pairs (Fig. XIX-C, non-significant interaction of trial and group: $F(1,32)=0.13$, $p=0.72$, $\eta p^2=0.004$).

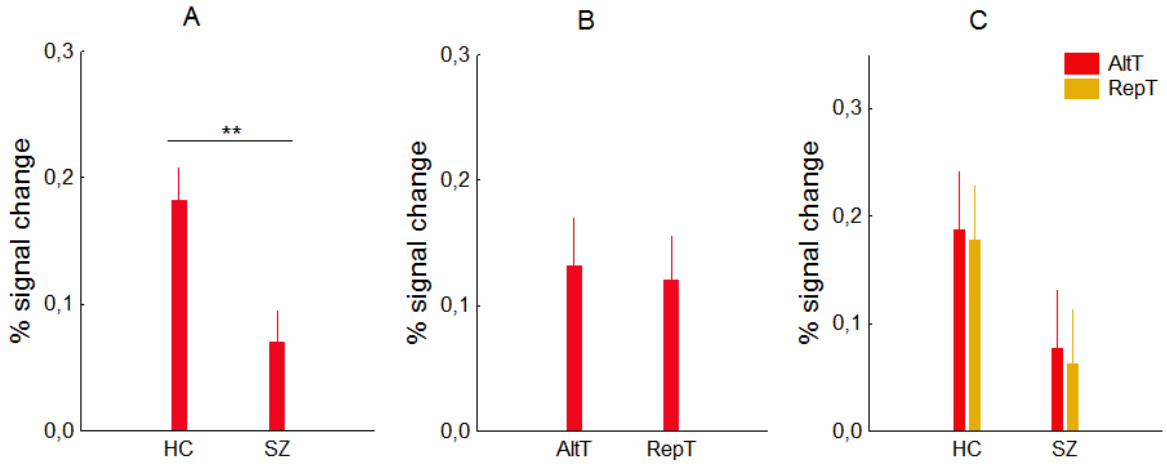

Figure XIX: A) Average peak activation profiles (±SE) of the LO in both groups separately, but averaged across hemispheres. Significant group effect. **p ≤ 0.01. **B)** Average peak activation profiles (±SE) in the LO for both trial types separately, but averaged across groups, hemispheres and blocks. Non-significant trial effect. **C)** Average peak activation profiles (±SE) of the LO for both groups and trial types separately, but averaged across hemispheres and blocks. Non-significant interaction of group and trial

Similar to FFA and OFA, the BOLD response was higher over the right compared to the left LO in both groups similarly (Fig. XX-A, significant main-effect of hemisphere: $F(1,32)=6.49$, $p=0.02$, $\eta p^2=0.17$; Fig. XX-B, non-significant interaction of hemisphere and group: $F(1,32)=1.88$, $p=0.18$, $\eta p^2=0.06$). Furthermore, the exhibited suppression levels in condition of repeated or alternated faces were not differing over the hemispheres (non-significant interaction of trial and hemisphere: $F(1,32)=0.76$, $p=0.39$, $\eta p^2=0.02$), as well the group-type had no further dependency (non-significant

interaction of trial-hemisphere-group: F(1,32)=0.55, p=0.47, ηp^2=0.016).

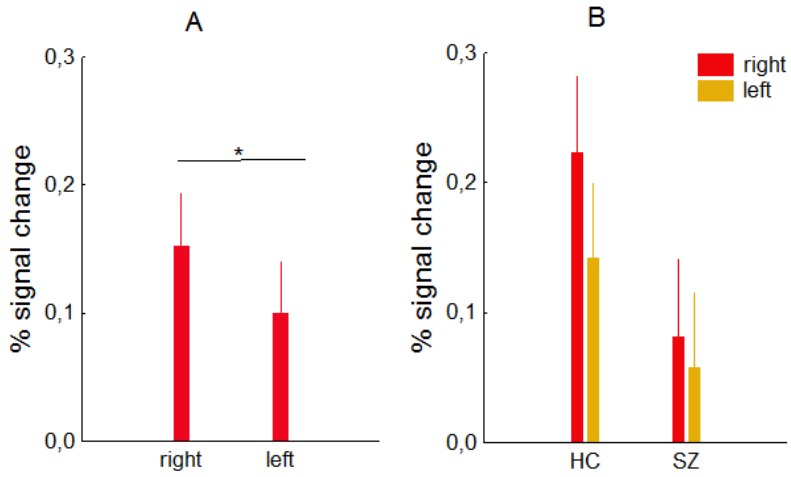

Figure XX: A) Average peak activation profiles (±SE) of the LO for the left and the right hemisphere separately, but averaged across groups, trials and blocks. Significant hemisphere effect.. *p ≤ 0.05 **B)** Average peak activation profiles (±SE) of the LO for the left and the right hemisphere separately for both groups, but averaged across trials and blocks. Non-significant interaction of hemisphere and group.

Repetition probability modulation

As in the face sensitive areas mentioned above, RS was strongly dependent on p(rep) in LO, as well (Fig. XXI-A, significant interaction of block-trial: F(1,32)=26.43, p=0.000013, ηp^2=0.45, Fisher's post-hoc test AltB: p=0.01, RepB: p=0.00007). Contrastingly to FFA and OFA, here was a slight influence of group type on the RS modulation effect, but separate analyses showed that the interaction of block-trial remained significant in each group (Fig. XXI-B, marginally significant interaction of block, trial and group: F(1,32)=3.90, p=0.06, ηp^2=0.11; Fisher's post-hoc test for SZ - AltB: p=0.46, RepB: p=0.02 and HC - AltB: p=0.0004, RepB: p=0.0003; separate analyses - significant interaction of block-trial in SZ: F(1,16)=7.0. p=0.02, ηp^2=0.3 and in HC: F(1,16)=19.8, p=0.0004, ηp^2=0.55). Consequently, the influence of group-type on the interaction of block and trial might possibly be explained by the small BOLD response level in SZ, compared to HC. Crucially, Fisher's post-hoc test showed the RS effect in RepB for both groups that could not be revealed in the simple trial effect in the LO before. Additionally, RE was found in condition of high frequent alternation, only in HC. The results suggest context-modulation of RS for both groups in the LO.

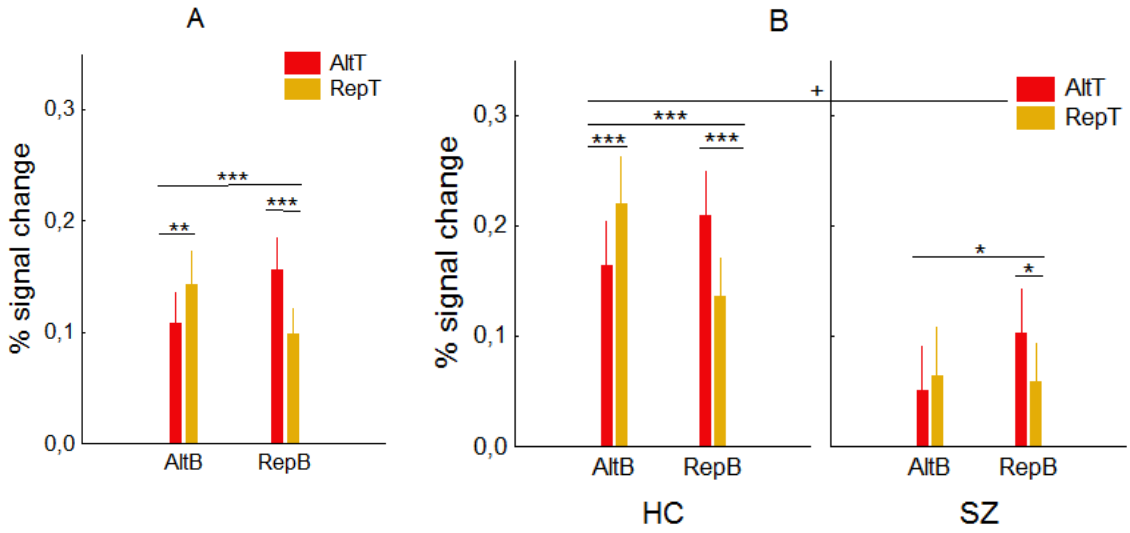

Figure XXI: A) Average peak activation profiles (±SE) of the LO for the AltTs and RepTs separately for each block, but averaged across groups and hemispheres. Significant interaction of block and trial. Significant RS in RepB and RE in AltB. **p ≤ 0.01, ***p ≤ 0.001 (Fisher's post-hoc test). **B)** Average peak activation profiles (±SE) of the LO for the AltTs and RepTs separately for each block and in dependency to the groups, but averaged across hemispheres. Marginally significant interaction of block-trial-group. Explorative analyses: significant interaction of block and trial and RS in RepB in each group separately. +p=0.09, *p ≤ 0.05, ***p ≤ 0.001 (Fisher's post-hoc test and interaction effect for HC and SZ in separate analyses).

The RSI analyses emphasised further the different BOLD responses in alternating or repeating blocks in both groups. In the high frequently repeating trials condition, RSI was much larger than in the compared condition. Furthermore, the RS effect with positive values in the RepB could be opposed to negative values in the AltB in both groups similarly (Fig. XXII-A, significant block-effect: $F(1,32)=12.2$, $p=0.001$, $\eta p^2=0.28$; Fig. XXII-B, non-significant interaction of block-group: $F(1,32)=1.6$, $p=0.22$, $\eta p^2=0.05$). Importantly, there was no main-effect of group for the RSI ($F(1,32)=2.44$, $p=0.13$, $\eta p^2=0.07$). Therefore the group-difference in the general analysis is revealed by a response magnitude difference only. The p(rep) modulating influence on RS phenomenon accounts for SZ in LO, as well.

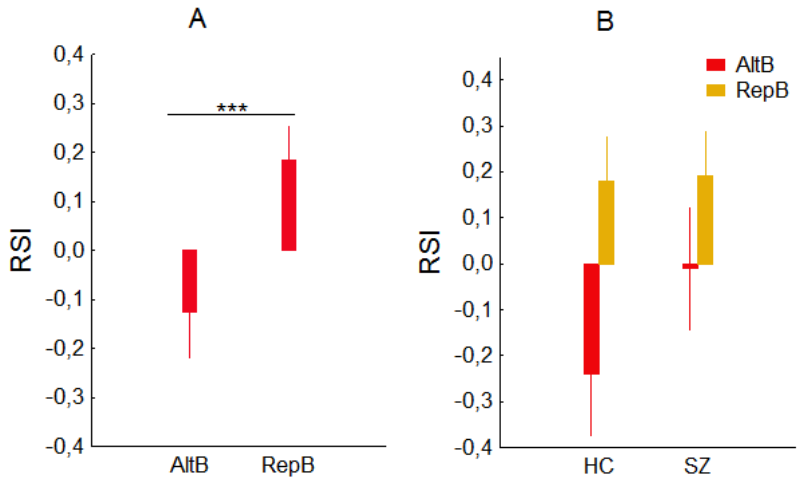

Figure XXII: A) The RSI of the LO for AltB and RepB separately, but averaged across groups and hemispheres. Significant block effect. Strong modulation of RS by p(rep) in the blocks in both groups. ***p ≤ 0.001. **B)** The RSI of the LO for AltB and RepB in both groups separately, but averaged across hemispheres. Non-significant interaction of block-group. Positive values indicate more pronounced responses in the AltT than in the RepT, negative values indicate the opposite (Kovács et al., 2012).

4.5. Whole brain analysis

Predictive functional runs

The whole brain analysis of the predictive functional runs was performed to test whether SZ and HC show different activation in brain areas other than the ROIs analysed above. Due to the region of interest-based approach in this study, it is possible that RS and p(rep) modulation of RS provoke further regions interacting in the brain. The second-level whole brain analysis was performed for the two groups separately. Testing the main effects of trial (AltT>RepT) and the main effect of block (AltB>RepB) did not reveal significant activations in either groups, neither with the commonly applied rigorous threshold of $P_{FWE} < 0.05$ (cluster size, k > 50 voxels) nor with the more liberal p<0.0001 one (cluster size, k >20 voxels). In SZ, testing the p(rep) modulation of RS in the F-test with the trial x block interaction (AltB_AltT vs. AltB_RepT) vs. (RepB_AltT vs. RepB_RepT) under the commonly used threshold of $p<0.0001_{\text{UNCORRECTED}}$ (MMN average cluster size [x,y,z], k > 20 voxels) revealed the following clusters (Fig. XXIII): ([38, -82, -14], k=25) which was in close correspondence to the left LO. Results are in accordance to our clusters in the functional localiser's second-level analysis (compare Fig. XXIV). Further activation clusters were found and attributed to the following areas: the right and left STG,

Brodmann area (BA) 22 ([60, -24, 0], k=20 │ [-62, -52, 14], k=162), right transversal temporal gyrus, BA 41 ([44, -28, 12], k=51), two areas in the left insula, BA 13 ([-30, -22, 14], k=29 │ [-24, -24, 22], k=28) and parahippocampal region, BA 19 ([-26, -56, -10], k=33). In HC, the p(rep) modulation of RS in the F-test with the trial x block interaction (AltB_AltT vs. AltB_RepT) vs. (RepB_AltT vs. RepB_RepT) under the commonly used threshold of $p<0.0001_{\text{UNCORRECTED}}$ (MMN average cluster size [x,y,z], k > 20 voxels) revealed: the left OFA and LO corresponding coordinates ([-40, -72, -4], k=585 │ [-38, -92, -6], k=121), the right and left lingual gyrus, BA 18 ([24, -76, -6], k=35│[-12, -86, 0], k=20), the left STG, BA 42 ([-54, -32, 12], k=201). Consistently with our previous findings, HC showed stronger activations, however in SZ somewhat more activation clusters could be identified (Fig. XXIII).

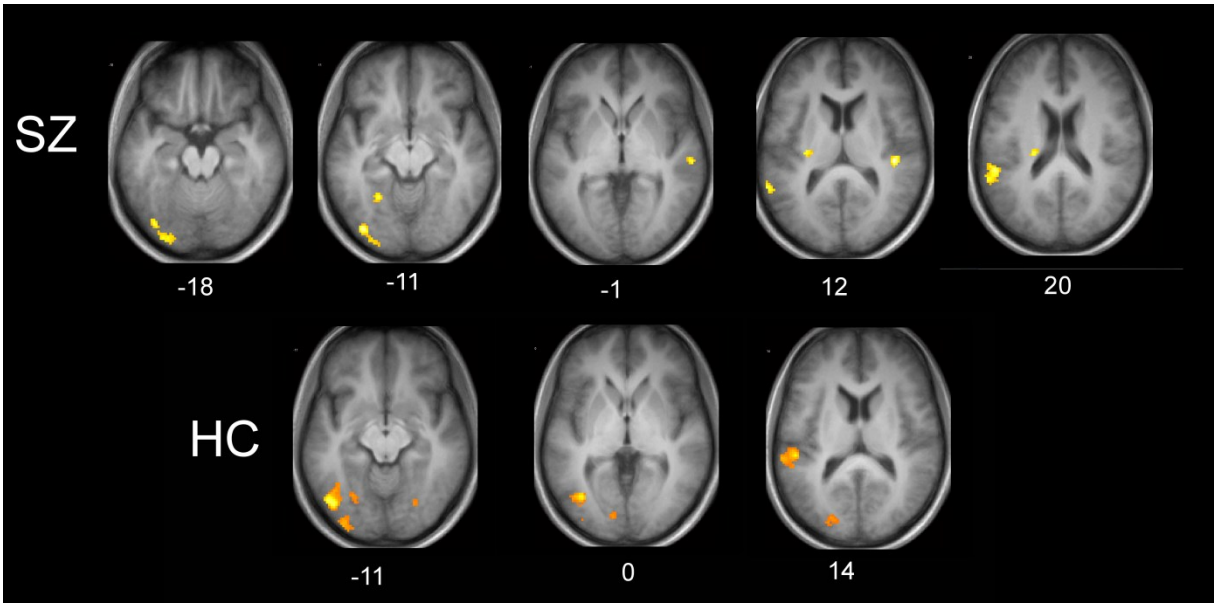

Figure XXIII: Whole-brain analysis of the functional predictive runs showing the areas activated while face processing and prediction of p(rep), HC and SZ groups separately. Identified regions ([z] slicing level) for SZ: LO (z=-18); parahippocampal region, LO (z=-11); STG(z=-1); right transversal temporal gyrus, left insula, left BA 22 (z=12); left STG, left insula (z=20); and for HC: lLO, lOFA, right and left lingual gyrus (z=-11); lOFA, lingual gyrus (z=0); STG, lingual gyrus (z=14).

Functional localiser

The whole brain analysis of the functional localiser served to visualise the identified ROIs from the individual first level analysis (compare with Fig. VI) in an averaged template of cerebral BOLD response while perceiving faces (Fig. XXIV). The

following clusters were found (under the commonly used threshold of $p<0.0001_{UNCORRECTED}$ and cluster size, k > 20 voxels) revealed in accordance to the ROIs computed in first-level analysis computed ROIs by considering all given contrasts of face, object and noise images. In SZ, the face perceiving areas were identified in clusters (MMN [x,y,z] average cluster size in voxels ±SE) of right and left FFA ([42, -52, -18] 68±10, [-42, -52, -18] 59±12), right and left OFA ([46, -78, -14] 51 ±8, [-38, -86, -16] 60±9) and the right and left LO ([38, -86, -4] 60±9, [-30, -98, 0] 52±9). In HC, the face perceiving areas were identified in clusters (MMN [x,y,z] average cluster size in voxels ±SE) of right and left FFA ([42, -50, -20] 51± 9, [-38, -42, -24] 50± 9), right and left OFA ([42, -78, -8] 61 ±11, [-42, -72, -12] 49±10) and right and the left LO ([40, -82, 0] 63±10, [-34, -92, 6] 55±7).

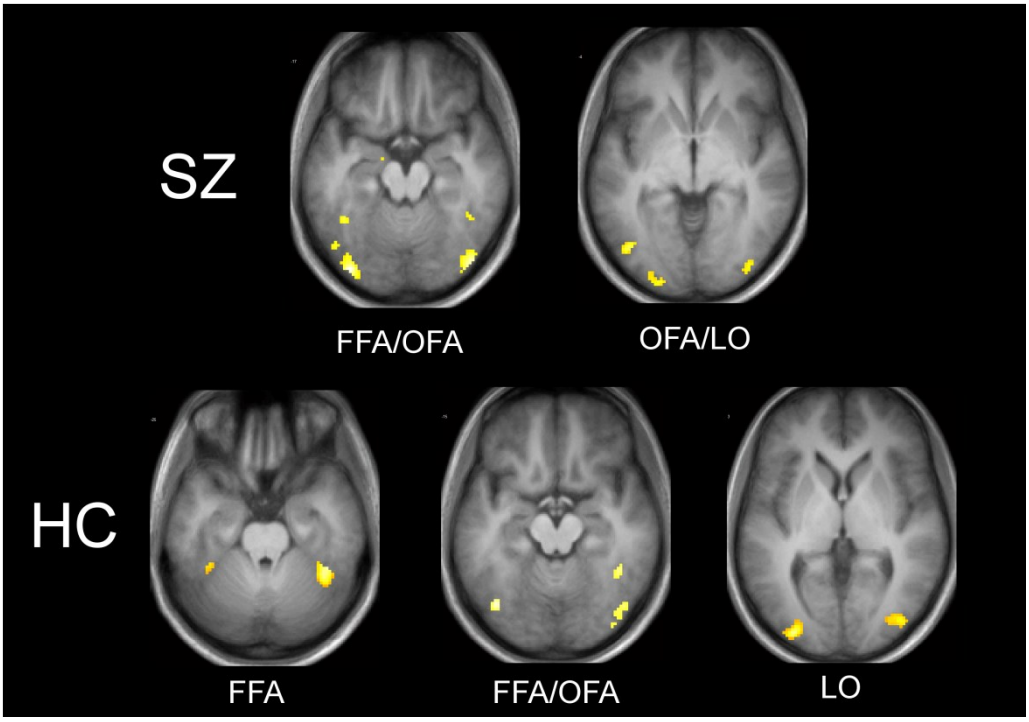

Figure XXIV: Whole-brain group results of the functional localiser determined in a second-level analysis showing the ROIs for HC and SZ groups separately. **SZ)** The average MNI coordinates with average cluster size in voxels (±SE) of both hemispheres, respectively: the FFA ([42, -52, -18] 68±10, [-42, -52, -18] 59±12), the OFA ([46, -78, -14] 51 ±8, [-38, -86, -16] 60±9), the LO ([38, -86, -4] 60±9) and ([-30, -98, 0] 52±9). **HC)** The FFA ([42, -50, -20] 51±9, [-38, -42, -24] 50± 9), the OFA ([42, -78, -8] 61 ±11, [-42, -72, -12] 49±10), the LO ([40, -82, 0] 63±10, [-34, -92, 6] 55±7).

5. Discussion

In line with the three hypotheses and the respective results, we aim to discuss the following key findings and their implications: 1) The key role of the FFA, lacking group difference for BOLD response to neutral face stimuli, and the reduced magnitude in the earlier face processing areas, OFA and LO, are evaluated based on previous studies. 2) RS found in patients with schizophrenia (SZ) is discussed in light of other repetition-related phenomena, such as habituation and repetition priming, emphasising the automatic, low-level characteristics of RS, preserved face selectivity, and partially intact salience distribution for schizophrenia. 3) The lack of group difference in p(rep) modulation of RS in the occipitotemporal cortex is differentiated from other methods testing predictive coding theory, such as mismatch negativity (MMN) and prepulse inhibition (PPI), with regard to the underlying neural mechanisms. The “dynamic high-level involvement” is hypothesised for the p(rep) paradigm to enlarge the storage capacities, compared to short-term transition of MMN (Wacongne 2016), but not reaching permanent involvement of higher-level areas as in conscious expectation (Grotheer and Kovacs 2016). In light of the whole-brain results, the p(rep) modulation network based on the interaction of the dual attention pathways and possible compensatory regions in SZ are discussed in the last chapter.

5.1. Analysis of general face processing

Altered earlier visual face processing

The result of lower BOLD signal magnitude in the OFA and LO suggests altered earlier visual face processing in SZ, as compared to HC. This finding is consistent with a previous fMRI study reporting reduced activation in the LO during visual backward masking (Green et al. 2009), but not with a study of object recognition that found similar activation for the LO in both groups (Wynn et al. 2008). Another study observed OFA’s activation level to be relatively normal, i.e. without significant group differences (Maher et al. 2015).

Visual backward masking is a method for assessing early perceptual processes (the first tenth of a second) when attentional effort has minimal effect (Rassovsky et al. 2005, Breitmeyer and Ogmen 2000). In the paradigm the visibility of a target (a gap

in a square) is disrupted by the occurrence of the visual mask (a composite of squares) presented briefly after the target. LO was attributed a key-role in visual masking and other integration deficits contributing to the functional outcome in schizophrenia (Green et al. 2009). The attributed sub-function of LO in the visual stream processing areas is to provide a representation of the visual shape (Vinberg and Grill-Spector 2008). A weaker unified representation of the stimulus was suggested due to a decreased response from LO (Green et al. 2009). It can be hypothesised that a weaker response to face stimuli argues for a weaker unified representation of the facial shape in the LO.

As the LO is a face and object processing area (Grill-Spector et al. 1999), a study investigating early processing of objects in schizophrenia can be compared with the face processing paradigm used here. Wynn et al. (2008) found a similar amplitude in the LO in both groups, and interestingly a broader topography of LO was observed as well. The abnormal spatial organisation was interpreted as a compensatory mechanism to set off impaired function, or lesser specialisation of the cortex in SZ (Wynn et al. 2008). In our study, the voxel size was measured in a functional localiser in SZ (k=60±9, k= 52±9) and in HC (k=63±10 and k=55±7) for right and left LO, respectively. Group-averaged voxel size for the LO does indicate a similar extent in the ROIs. Our findings showed a decrease in BOLD-response to faces (which might also reflect a decrease in function), but no specialisation deficit. LO is sensitive to faces (even with less amplitude).

In the study of Maher et al. (2015) groups did not differ regarding the BOLD response on tree and face presentation. Thus, face selectivity was demonstrated in the OFA for SZ as well. Therefore, it can be concluded that reduced OFA response to faces is an inconsistent finding and should not necessarily be interpreted as face selectivity impairment in this area. The consequences of reduced face response of OFA and LO are discussed below.

LO and OFA function – a temporally dissociated ventral visual stream

Both regions showing decreased response magnitude are sub-regions of the LOC, thus in the lower-level ventral visual stream, which was predicted to be less disturbed than the dorsal visual stream in SZ (Ungerleider 1982, Malach et al. 1995, Butler et al. 2001). Foxe et al. (2005) suggested ventral stream processing to be essentially

normal, but temporally diverted in two stages, whereas only the first stage of processing is fully intact. This might explain why the response magnitude in OFA and LO was diminished in SZ, but not totally erased – a temporal dissociation of function. Foxe et al. (2005) established the hypothesis of a temporal two-stage model using illusory contours in visual evoked potentials: the first stage of processing was essentially normal (140-200 ms, N1 - feature processing (Tobimatsu 2012)), whereas the second stage (240-400 ms, negativity for closure (N_{cl})) was severely impaired. A critical modulating input from the dorsal visual stream was hypothesised to disturb the ventral processing only in the second stage representing "perceptual closure" (Doniger et al. 2002), the filling-in of missing information as only fragments were processed before (Doniger et al. 2001, Foxe et al. 2005).

In our paradigm a stimulus was presented only for 250 ms, nevertheless it might be possible that the BOLD response reduction of OFA and LO resulted from a disturbing dorsal stream influence during the "second stage" of processing. Silverstein et al. (2010) support this hypothesis describing a dorsal visual stream influence on PFC, resulting in reduced ventral visual stream activation. Crucially, the BOLD response was not totally erased due to an intact "first stage" processing in the ventral visual stream. The impairment in "perceptual closure" (Doniger et al. 2002) as the ability to fill in missing information to the degraded "puzzles" that were sent from the retina, is in line with the notion of a "weaker unified representation" of stimuli in schizophrenia (Green et al. 2009).

Functional consequences of altered face processing in earlier stages

The alterations in earlier face processing stages are potentially linked to specific aspects of function of the OFA and LO. Frith et al. (1983) already declared a general 'gestalt' perception deficit in schizophrenia. Recent findings show that this assumption might be too general as 'gestalt' perception comprises configural and holistic processes. The latter was shown to be used as mechanism in SZ, but not sufficient for optimal face processing (Watson 2013). Recent studies found deficits of face processing in schizophrenia only for configural perception (Shin et al. 2008, Joshua and Rossell 2009), the ability to perceive the relational properties (Piepers and Robbins 2012). The LO and OFA processing deficits might mirror these findings. Previous studies have attributed the detection of second order configural cues (Rotshtein et al. 2007) and the composition of holistic cues to a global representation

to the OFA (Ramon and Rossion 2010). Disturbed LO in schizophrenia was associated with a weaker unified representation (Green et al. 2009). Partial face processing deficits in OFA and LO might contribute to the configural perception disruption in schizophrenia, and thus to a social percpetion deficit mediating the functional outcome (Sergi et al. 2006).

There are studies reporting an intact configural processing (Schwartz et al. 2002) or an over-reliance on featural face encoding (Joshua and Rossell 2009). Feature-processing is reflected in the "first-stage" of the model of Foxe et al. (2005) with an intact response character in the ventral visual pathway. Moreover, these insights might rely on intact FFA processing, as we found BOLD response in SZ being similar to HC.

Intact FFA functions – concurrent and contrasting literature

The FFA was found to be an intact key-component in the perceptual processing of faces in schizophrenia (Yoon et al. 2006). It is specialised in face detection and recognition (Kanwisher and Yovel 2006). Our results of intact FFA function in SZ diverge from other fMRI studies (Quintana et al. 2003, Habel et al. 2010, Walther et al. 2009). The difference in the response characteristics of the FFA may be related to abilities conveying tasks demanded. In common with the study of Yoon et al. (2006), our behavioural task was relatively easy resulting in high-level performance in both groups, whereas Quintana et al. (2003) required the monitoring of three stimuli simultaneously in their tasks. It was previously reported, that when tasks were simple, deficits in processing could be compensated (Quintana et al. 2001, Quintana et al. 2003). Our task did not demand memorising and identification of individual faces, so the simple face size recognising task did not overtax such compensatory mechanisms.

In a study with SZ, face processing abilities were dissociated: face detection of a briefly displayed face was significantly reduced ($p=0.003$), whereas face identity discrimination showed only the tendency for a group difference ($p=0.065$) (Chen et al. 2009). These findings support our results indirectly: function disturbance of the earlier face processing abilities that are attributed to OFA and LO, whereas FFA's response was similar to HC.

Results of hypoactivation in the FFA were also found in a study investigating face

recognition, and identifying of famous, familiar and newly learned faces (Walther et al. 2009). These higher-level abilities of the FFA were not aimed to be tested in our study.

Habel et al. 2010 directed attention to emotional expression whereas the interacting network of areas processing emotion is accepted to be abnormal (Holt et al. 2006, Li et al. 2010). Thus, the hypoactivation of the FFA in former studies comparing neutral to other facial expressions might be the result of divergent incoming or higher order information from severely impaired regions in schizophrenia (Fairhall and Ishai 2007).

More importantly, the present study showed that earlier stage deficits in OFA and LO during the encoding of faces probably cause impairments of face processing in schizophrenia. This finding responds on Yoon et al. (2006) demanding of investigations on the general status of the wider face processing network in schizophrenia and it supports Walther et al. (2009) assuming early-stage deficits.

FFA and OFA interactions in the face processing network

To point out the major role of the FFA, the interaction with OFA are analysed regarding the different response characteristics in our study. Based on data obtained from studying prosopagnosia patients, Rossion et al. (2003) and Steeves et al. (2009) proposed that the regions were not strictly hierarchically depending on each other. Patients with OFA damage showed a normal range of sensitivity to faces in the FFA, and thus an OFA-bypassing route was proposed allowing information flow directly to the FFA (Steeves et al. 2009). This model gained support since categorisation abilities could be achieved even with lesion in the OFA and an interactive model was suggested enabling high-level face perception (Atkinson and Adolphs 2011).

The results of a weaker OFA response, normal FFA response in schizophrenia support an interactive model (Atkinson and Adolphs 2011) and the theory of OFA-bypassing routes (Steeves et al. 2009). The low BOLD response of the OFA did not disturb FFA's response characteristic and not even the higher-demanding abilities of face processing (i.e. RS modulation by p(rep)). Possibly, FFA could even compensate certain irregular response characteristics of OFA and LO to preserve basic functions as RS in schizophrenia (compare Silverstein et al. (2010), suggesting compensation of disturbed integration abilities with relatively increased FFA activity).

Sufficient attention during task and face processing

It is worth mentioning that the BOLD response could have been confounded as well by inattention to the stimuli (Gazzaley et al. 2005). However, our results indicate similar performance in both groups: reaction time on all conditions did not differ between groups, a run effect was found similarly for all subjects. Regarding accuracy in detecting the target stimulus, SZ even showed a tendency to perform better, the run effect was not observed for accuracy in target detection. Thus, attention effects did not seem to diverge between groups. The behavioural outcome of our two participant groups is also comparable with a previous study of Grotheer et al. (2014), using the same task and revealing similar results in another cohort of healthy subjects.

Hemispheric symmetry or asymmetry

Finally, it seems important to briefly evaluate the lateralisation effects in the BOLD response for face stimuli in the comparison between groups. Our results indicate similar lateralisation to the right in both groups, with exception of the OFA of SZ being equally responsive in both hemispheres. This is in contrast with the reports on generally reduced lateralisation in SZ (Bourne and McKay 2014) and a right-sided deficit in attentional functions being independent from face processing (Kucharska-Pietura et al. 2002). Interestingly, Bourne and McKay (2014) suggested patterns of lateralisation being atypical for emotional stimuli. We can confirm this for face stimuli.

5.2. Analysis of the RS phenomenon

Repetition suppression (RS) as a consistent finding in schizophrenia

We found RS (as a BOLD response attenuation in the condition of highly probable repetitions) in both groups. This result argues against the hypothesis of disturbed RS in schizophrenia *per se* as based on the above-mentioned assumption of salience processing irregularities in schizophrenia. However, intact RS is consistent with a study reporting intact local visual processing in the FG for normal and transfigured faces (Bleich-Cohen et al. 2009), another study observing intact repetition priming in FG (Schwartz et al. 2013), and a third finding with intact habituation in the FFA (Williams et al. 2013). We are not aware of any comparable studies investigating

OFA and LO for repetition effects in SZ. Thus, the finding of intact RS in OFA and LO is novel in SZ. This is remarkable since the BOLD response magnitude in these areas was found to be significantly lower than in controls. Nevertheless the repetition selective characteristic of neurons seems to be preserved.

Several studies support this finding. The first study reported intact habituation in the FFA (Williams et al. 2013), which is comparable to RS (Rankin et al. 2009). Additionally, they reported deficits in hippocampus and primary visual cortex (PVC) and suggested that habituation occurs in different brain regions relatively independently. This notion is supported by our findings of intact RS in the three investigated areas, including the FFA. Another study by Bleich-Cohen et al. (2009) suggested normal face processing following a comparison of first-episode SZ and HCs, even when connectivity of FG with amygdala and PFC was reduced. Obviously, deficient connectivity with higher cortical areas does not disturb the suppression effects after repetition. Therefore we may argue that RS is relatively independent from higher cortical influences and processed on a lower (and automatic) level (Grotheer and Kovacs 2015). The automaticity of the RS phenomenon was confirmed as the attention was diverted from repetition (here: button-press for size deviance) (Larsson and Smith 2012). RS is assumed to be an implicit process without higher-order control (compare Ward et al. (2013). Another repetition priming study, using faces as stimuli under the same premise, found that the effect is implicit (Schwartz et al. 2013). Implicit priming was preserved in schizophrenia, as well as the activation in the right FG, while only the left FG showed reduced neural response for repetition priming.

From RS to associative salience

With regard to RS as a selectivity-assigning phenomenon, we hypothesise that the face selective response character of the investigated regions (with LO as face and object-selective area) is preserved in SZ. There is one study reporting on a lack of face selectivity versus trees in the FFA in schizophrenia (Maher et al. 2015). Interestingly, these authors found this dysfunction to be dependent on the perceptual contrast, i.e. only when contrast levels were low the selectivity dysfunction occurs. This might be an additional aspect underlining the deficits of “perceptual salience” in schizophrenia, i.e. to perceive the sensual prominence of an object due to its

physical low-level properties (colour, contrast, intensity) (Santangelo 2015, Trevino 2015). The face selectivity as an ability to perceive faces as repeated/familiar or novel/salient and to distinguish faces from objects seems to be basically intact in schizophrenia. The ability of attentional selection to certain stimuli as faces, was recently shown to induce a prioritisation in processing (Downing et al. 2004). Perceptual salience was investigated by contrast-levels in face perception (Maher et al. 2015), by surround suppression of perceived contrast (Schallmo et al. 2015), and by colour intensity changing of faces (Esslinger et al. 2012). This might be a confounding factor of face selectivity.

Thus, RS should be distinguished from perceptual salience and might rather refer to a type of “associative salience”, i.e. attribution of values to stimuli to increase effectiveness in processing (Trevino 2015). In our paradigm the physical properties, such as contrast and luminescence were equalised for all stimuli, thus perceptual salience can be excluded as a factor in determining the salience processing in SZ. Another study investigated face response to famous vs. infamiliar faces (Esslinger et al. 2012) and proposed to assess ‘associative salience’ that is based on increased strength of memory traces occurring during repetition (Menon et al. 2005). Our results revealed a similarly reduced activation for repetition/familiarity and increased activation for novelty/unfamiliarity (compare Esslinger et al. (2012)). Therefore “associative salience” might be a better notion to conceptualise RS in our patient data. Our findings of intact RS for faces in FFA, OFA and LO might be due to the use of face stimuli that are processed in the rather intact ventral visual stream (compare (Parsons et al. 2013, Williams et al. 2013).

Repetition enhancement as completing phenomenon to evaluate salience

One novel finding of our study is the enhancement of neural response when probability for repeating faces was lower. Repetition enhancement (RE) describes an increased BOLD response from AltT to RepT in condition of unlikely repetitions (i.e. AltB), compared to RS in a condition of highly likely repetitions (i.e. RepB); thus RE and RS are contradictory in response character. A tendency for RE was found in the FFA, it was significant in the OFA for both groups, and in the LO for healthy controls only. Previous studies with a comparable paradigm did not show RE (Summerfield et al. 2008, Kovacs et al. 2012, Grotheer and Kovacs 2015, Grotheer et al. 2014).

Nevertheless, it is likely to detect an enhanced signal for a suddenly occurring trial of repeating faces in the course of alternating face pairs (i.e. AltB). The enhancement of BOLD signal can be explained with a missing stable memory representation of novelty (Segaert et al. 2013). In priming research, RE is observed for unfamiliar or difficult-to-recognise faces (Henson and Rugg 2003) and surprise is considered as a negative probability of the sensory input in the concept of perceptual prediction (Sedley et al. 2016). Kovacs et al. (2012) already mentioned a surprise related elevation of BOLD response referring to the original definition of Rao and Ballard (1999): violated predictions in the case of AltT in the RepB led to signal elevation. It was previously observed in the V1, FFA, and hippocampus (den Ouden et al. 2009, Egner et al. 2010, Strange et al. 2005). The underlying mechanisms are supposed to reflect prediction and ε, similarly to RS (Segaert et al. 2013). RS and RE are thought to be independent from expectation, thus not necessarily involving higher order regions (Grotheer and Kovacs 2016).

In summary, we need to consider “repetition effects” including RE when discussing the context of associative salience. The salient character of the face stimulus might be indicated by RE. Both effects together assign the ability to connect associations. Associative salience seems to be relatively preserved, i.e. RS in all areas investigated and RE in FFA, OFA in schizophrenia.

5.3. Analysis of p(rep) modulation on RS

Intact prediction error encoding in SZ

Central to this study’s aims, the modulation of the RS phenomenon by p(rep) of face stimuli was found to occur without significant difference in the face processing regions of both schizophrenia patients and healthy controls. RSI presented consistently positive values in RepB, opposed to negative values in AltB. Thus, an increasing RS effect in case of highly likely repetitions indicates a context-dependent modulation effect. Stimulus probability effects for faces have been studied in healthy subjects before and assumed to reflect predictive coding (Summerfield et al. 2008, Kovacs et al. 2012, Grotheer et al. 2014). However, correct ε estimation in the visual face processing areas in schizophrenia patients is a novel finding. All areas investigated showed a lack of group difference in p(rep) prediction effects, only LO

showed a marginally significant dependency of the group-factor that was found to arise from a strong RE in HC and general lower BOLD signal in SZ (see Figure XXV-B). There was no influence of OFA's BOLD response attenuation on the higher order effects. The unconscious prediction of face repetitions under correct ε estimation is supposed to be preserved in the occipitotemporal cortex in schizophrenia.

Studies proposing prediction impairments in SZ

Prediction impairments have been studied with different methods, at times resulting in seemingly contradicting findings. We therefore aim to compare our findings to these approaches, taking into account comparability and achieved level of prediction processing. Methods investigating prediction as cognitive functions in schizophrenia (Butler et al. 2012) were previously emphasised in their clinical relevance by CNTRICS, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia: corollary discharge, mismatch negativity (MMN), and prepulse inhibition (PPI). All methods would refer to "gain control", a model assuming optimisation of response with respect to the temporal context. Neurons interact, attenuate the signal, and achieve a global, more complex structure, thus "sensory integrity". fMRI was proposed to reflect "integration" as well as a method linking the output of neurons with a complex structure "more suitable for guidance of behaviour" (Butler et al. 2012).

PPI – High-level involvement rather attention dependent

PPI is a method to identify "sensorimotor gating" of the startle reflex to strong, sudden acoustic or tactile stimuli (Butler et al. 2012). Through the prepulse, an attenuated, unconscious stimulus immediately preceding the main stimulus, diminishes the startle reflex (Butler et al. 2012). It is yet another method to reflect adaptation of neural systems to a general context showing impaired functional status in schizophrenia (Swerdlow et al. 2006). PPI is impaired in intramodal- and crossmodal-gating (e.g. acoustic or tactile prepulse) in schizophrenia (Braff et al. 1992). The underlying cerebral mechanisms rely on be local process in the ascending auditory system as the centre for interacting sensory modalities (Koch 1999). But there is also evidence to suggest PPI to be a higher order controlled process: inhibition of sensory/motor events, i.e. the startle reflex, is based on the organisation of the sequential behaviour and thus, a PET study found prefrontal

activity in BA 8,9,10 in healthy controls, whereas schizophrenia patients showed increased signal only in left BA 10 (Hazlett et al. 1998). Hazlett and Buchsbaum (2001) connected this reduced prefrontal activation with the observation of attentional modulation of PPI. They observed a lack of higher frontal activation during attentional modulation in unmedicated patients. We conclude on a relevant influence of attentional processes on PPI. Moreover, abnormal automatic activity was observed during the eye-blink response in SZ (Hazlett and Buchsbaum 2001). Further evaluation is needed to assure PPI representing an automatic processing deficit or a higher order control deficit. There are, to our knowledge, no PPI studies involving the visual modality, therefore PPI cannot be compared with our findings.

Corollary discharge – a threefold deficit exceeds compensatory mechanisms

The corollary discharge concept is another forward model suggesting the interaction of two systems (such as motor cortex and auditory cortex) to define “self” and “non-self” (Frith and Done 1988). The “efference copy” from the motor command is used to generate a neural representation of the expected sensory consequences in the sensory areas. The comparison of the sensory afference with this expected representation matches for self-generated movements (Whitford et al. 2012). Self-perception of physical movements (Frith et al. 2000, Shergill et al. 2005, Shergill et al. 2014) and voice-perception during one’s own speech (Ford and Mathalon 2012) were found to be impaired in corollary discharge experiments in patients with schizophrenia. Corollary discharge was supposed to validate the inability to predict sensations (Ford and Mathalon 2012). The ability to suppress sensations resulting from our own actions are supposed to be processed in a lower automatic level of interacting areas such as motor and auditory regions (Butler et al. 2012). But abnormalities in frontal myelination have also been made responsible for conduction delays for frontally generated efference copies and posteriorly represented corollary discharge, ultimately resulting in a mismatch with the real sensory afference (Whitford et al. 2012). Additionally, corollary discharge includes mirror neuron activity, thereby reflecting social cognitive function as a distinction of one’s own and other’s action (Murata et al. 2016); the parietal and premotor cortex are assumed to generate and send efference copies. Interestingly, this network is anatomically connected with the dorsal and ventral visual stream: the ventrodorsal pathway passes the anterior intraparietal area (AIP), the intraparietal sulcus and the PFG on

the lateral posterior parietal cortex (Rizzolatti and Matelli 2003). Thus, mirror neurons are always driven by visual feedback. Quintana et al. (2001) found motor and premotor areas showing an enhanced neural representation of facial expression in schizophrenia, also interpreted as a compensatory mirror mechanism of observed face expression, and additionally frontal-limbic dysconnectivity. The basic deficit of the sensory system, plus a dysconnection might possibly go beyond the "compensating mirror activity". In our paradigm, the frontal connections (Whitford et al. 2012) might be the same as proposed for corollary discharge and might be disturbed similarly. However, basic face processing seems to be intact (Foxe et al. 2005, Butler et al. 2001, Williams et al. 2013) or otherwise compensated (Silverstein et al. 2010). An involvement of compensatory connections from parietal/premotor regions to ventral visual pathway (Rizzolatti and Matelli 2003) would explain the lack of difference in p(rep) modulation of RS compared to HC in our paradigm. Certainly, network capacities seem to be sufficient during p(rep) modulation, but not during corollary discharge. Consequently, prediction processing deficits in corollary discharge reflect a threefold cause: basic sensory processing deficits (Ford and Mathalon 2012, Shergill et al. 2014), frontal deficits associated with dysconnection (Whitford et al. 2012), and possibly an exceeded capacity of mirror neurons (compare Quintana et al. (2001), Murata et al. (2016)).

MMN - local auditory deficits and a local-layer PC model

Mismatch negativity (MMN) has frequently been assessed in schizophrenia. The deviant (infrequent) stimulus in a stream of standard (i.e. frequent) stimuli provokes a mismatch response in event related potential (ERP) measurements (Csukly et al. 2013). A smaller amplitude after pattern deviance is a consistent finding in studies of auditory MMN in schizophrenia (Todd et al. 2014), and is frequently interpreted as a signal of deficient predictive coding (Naatanen and Winkler 1999, Todd and Robinson 2010, Friston 2012, Todd et al. 2012, Csukly et al. 2013, Lakatos et al. 2013, Neuhaus et al. 2013, Baldeweg and Hirsch 2015). MMN has been proposed as a brain marker for identification of different stages of psychosis (Nagai et al. 2013) and as a correlate of NMDAR pathology (Todd et al. 2014). Also, visual MMN (vMMN) appears to confirm prediction deficits in SZ (Urban et al. 2008, Farkas et al. 2015) and is similarly interpreted in the exploration of context-based prediction processing (Kimura et al. 2012). A comparison of local auditory (in STG) and visual

face processing areas (in ITG and FG) shows that structural gray matter deficits exist in both systems: STG decrease (Honea et al. 2005), inconsistent ITG decrease in VBM, but functionally significant in the posterior ITG in fMRI (Kuroki et al. 2006), and reduced FG in a post-mortem study (McDonald et al. 2000). Regarding function, the ventral visual stream is supposed to be rather intact (Butler et al. 2001, Foxe et al. 2005), whereas schizophrenia patients show early sensory processing deficits in audition (Javitt and Sweet 2015), acoustic segmentation deficits that are thought to result in higher-order deficits (Coffman et al. 2016), and reduced auditory-insula connectivity being critical in MMN (Kantrowitz et al. 2015). Thus, local auditory deficits seem to be crucial in MMN studies. Nevertheless, PC is accepted as an underlying mechanism (Garrido et al. 2009, Winkler and Czigler 2012, Wacongne et al. 2012, Lieder et al. 2013). Interactions between several levels of the cortical hierarchy adapt ε to assure the most likely cause of input (Friston et al. 2003). Interestingly, Wacongne et al. (2012) described a local-layer PC-model in the auditory region: dynamic interaction between predictive and prediction layers lead to minimisation of prediction and ε. Future stimuli are anticipated based on transition statistics that is encoded in the NMDAR-dependent synaptic strength between the highest predictive layer and the memory neurons of the short term memory. Wacongne et al. (2012) proposed that only sequences exceeding transition probabilities would involve higher-order neurons. Crucially, Wacongne (2016) showed in an adapted version of “NMDA-R impaired model” for SZ, that synaptic habituation and predictive processes contribute both to the MMN reduction.

MMN - imprecision in feature encoding, no general prediction impairment

Alternative interpretations of MMN dysfunction should be considered. There is evidence to understand the reduced amplitude in MMN as imprecise feature encoding (Todd et al. 2012): for SZ the current input was not sufficiently distinctive from prior input. This proposal includes a reduced dynamic range for schizophrenia in which the brain can represent the environment; consequently the brain is more frequently alerted since the events reach the maximal impact more often (Todd et al. 2012). Applying the hypothesis of imprecise feature encoding to our findings, it can be concluded that the stimuli were cued in a manner that they were sufficiently distinctive from each other. Modulation of RS via p(rep) is thought to be “strategic” (Ewbank and Henson 2012) in the block-arrangement with a dominance of either AltT

or RepT in a relation of 3:1, a relation that was found to be necessary to reveal a block-dependency of RS (Summerfield et al. 2011). The increased time-period of building-up an expectation on repetitions (in case of RepB) possibly balances an imprecision in feature-encoding, and thus preserves perceptual prediction. Another possibility is that the paradigm of p(rep) modulation does not assess these insensitivities in contextual differences described by Todd et al. (2013) to be reflected in MMN amplitude aberration. Our paradigm did not test the size and frequency of the deviant, that is observed in MMN with large and rare deviants comparing to small and frequent deviants (Todd et al. 2013). Thus, the detailed characterisation of deviant stimuli might be disturbed in schizophrenia, but not the contextual modulation or the recognition of "strategic" environmental settings.

The oddball-sequence, as an event-related paradigm with a continuous stream of repeating stimuli interrupted by an infrequent one, is commonly used in MMN and differs strongly from our mixed-paradigm with pairs of stimuli in p(rep) modulating blocks. There is another study-design of auditory MMN supporting the hypothesis of necessary cuing to overcome the imprecision in feature encoding and to challenge the prediction abilities in schizophrenia, the „linked sequence" (Nousak et al. 1996): a deviant is always followed by a second deviant (OOOOXX). Indeed, MMN amplitudes to anticipated deviants, although smaller in SZ, were no longer significantly different from those of the control groups (Todd et al. 2014). The comparison between a random versus a linked deviation is supposed to provide an „index of integrity of perceptual inference"(Todd et al. 2014). This approach is in line with our suggestion to distinguish lower (oddball sequence, simple RS) from higher stages of predictive processes (linked sequence-MMN, p(rep) modulation of RS) (Todd and Robinson 2010, Grotheer and Kovacs 2016). The results of later paradigms indicate that the repetition pattern makes best use of the limited dynamic signalling range. Interestingly, Todd et al. (2014) conducted an additional computation to avoid predominance of feature-based perceptual prediction and pointed out that there is no lack of prediction in schizophrenia per se. The presented findings place our study in a group of context-depended paired stimulus paradigms that demonstrate no severe impairment in prediction processing in schizophrenia.

High information value of the stimulus – definitive prefrontal involvement

In the study of linked-deviant in MMN the salience to the stimulus is increased (Todd

et al. 2014). The pairing of the deviant with a second deviant stimulus can be understood as higher information value (Todd et al. 2011) that could have stimulated prefrontal brain regions with greater capacity to reflect event probabilities (Kiebel et al. 2008).

Another condition involving higher order control is emotional stimulus processing. This was tested in a vMMN study with faces, where, again, SZ showed deficits in prediction processing (Csukly et al. 2013). The source of the mismatch responses to happy and fearful faces was indicated in frontal areas where SZ exhibited reduced activity. Crucially, expression-related MMN (EMMN) demands not only higher order functions for the prediction, but additional activation of emotion processing areas as well. The extended network of prediction processing areas (Williams et al. 2004, Holt et al. 2006, Li et al. 2010) might be an additional reason for deficits of prediction ability (Csukly et al. 2013). In the temporal-basal ganglia-prefrontal cortex system even simple emotional-face processing showed hypoactivation (Li et al. 2010). Kimura et al. (2012) have described the temporal, frontal, limbic and occipital lobe as generators for EMMN prediction processing in healthy subjects. Thus, it might be the emotional component, not necessarily the visual face prediction that exceeds beyond the capacity of the connecting system in schizophrenia.

5.4. "Dynamic high-level involvement" hypothesis

The discussion above supports the assumption of a two-stage model for prediction processes (Grotheer and Kovacs 2015, Grotheer and Kovacs 2016) that assumes RS and expectation suppression (ES) to be independent. Moreover, RS is thought to reflect a low-level process generating a local prediction error and communicating within the layers of the level. Only when conditions demand 'higher-regulating' areas, an expectation is built up and sent to 'lower' visual regions (see Wacongne et al. (2011)). What might be those conditions? Conditions of complex stimulus pattern, such as linked-sequence in MMN (Todd et al. 2014), and emotional face prediction (Csukly et al. 2013). Additionally expertise on stimuli and consciousness of pattern are possibly influencing parameters to achieve higher-level prediction.

Hierarchical stage model – allocation of p(rep) modulation

We suggest that high-level involvement is more likely when processing regions are sensitive, i.e. processing of stimuli to which participants show expertise is facilitated (Grotheer et al. 2014). The context-based modulation of RS by p(rep) was proposed to depend on expertise: in healthy subjects, the effect was observed with faces (Kovacs et al. 2012), but not shown with unfamiliar false fonts (Grotheer et al. 2014) and objects in the same paradigm (Kovacs et al. 2013). In our study, the effect was shown in SZ suggesting preserved expertise to faces despite cognitive impairments. Another relevant condition might be the 'unconscious' prediction processing in our paradigm, since subjects were not informed about a sequence of repetition. The recent term of ES reflects 'conscious' prediction in the manner that female faces signalised repetitions and male faces alterations (Grotheer and Kovacs 2015). ES was proposed as a conscious, high-level process, whereas RS was suggested to be necessarily unconscious (Grotheer and Kovacs 2016). Grotheer and Kovacs (2016) casted doubt on the high-level nature of 'unconscious' predictions. Also the MMN experiment of Bekinschtein et al. (2009) supported the necessity of conscious processing (i.e. higher order involvement) to predict longer sequences.

If assuming the two-stage model of independent low-level RS and continuously high-level involving ES (Grotheer and Kovacs 2016), our paradigm might reflect a "dynamic high-level involvement" (Fig. XXV). "Dynamic functional coupling" was previously proposed by Fairhall and Ishai (2007) as a content-specific alteration of connectivity in the visual-limbic and visual-prefrontal pathways during emotional and famous face processing in healthy subjects. The dynamic involvement assumes that continuous high-level involvement might be spared to optimise processing in terms of energy use (in the sense of Friston (2010)), as long as local layer-prediction mechanisms encode the stimuli sufficiently (see Wacongne (2016)). The hypothesis is that the network capacities in SZ might be sufficient when fewer requests demand the activation of prefrontal areas. The dynamic involvement might allow the recognition of the increased probability of repetition relatively early in the sequence and from then on controls the pattern only intermittently. Dynamically increased connectivity during execution of the p(rep) task would induce a kind of "stand to attention" position of the higher order prediction areas during highly probable repetition sequences. This notion is supported by findings by Chaumon et al. (2009) describing enhanced magnetoencephalographic (MEG) gamma band oscillations in a fronto-temporal band during conscious and unconscious contextual processes.

Gamma band activity disappeared when learning affected behaviour, i.e. processes were facilitated. Thus, high-level involvement might serve to facilitate behavioural improvement and therefore dynamic (in contrast to continuous) interaction is sufficient.

P(rep) network influenced by attention systems

The results of prior studies showing attention dependent higher-order involvement indicate this topic to be relevant in prediction processing. The parietal attention regions, right MFG and BA 7, were identified in the whole-brain analysis of conscious ES with healthy participants (Grotheer and Kovacs 2015). In PPI studies, deficits in SZ are thought to rely on deficits in MFG and DLPFC, regions that are involved in attention attribution as well (Hazlett and Buchsbaum 2001), and in MMN higher order involvement was considered to rather be dependent on attentional and behavioural shifts than to deviant detection (Gaebler et al. 2015). With the objective to identify possible key-regions in the p(rep)-network and to approximate the neural mechanisms of “dynamic high-level involvement”, the dual-stream attention system is analysed.

The dorsal network (intraparietal sulcus (IPS), frontal eye field (FEF), visual cortex) is supposed to build the top-down connections to sensory regions (Vossel et al. 2014), crucial during search and detection by cue-induced attention, spatial attention, visual working memory (Corbetta and Shulman 2002, Jerde et al. 2012, Vossel et al. 2014). The ventral network (temporoparietal junction (TPJ), ventral frontal cortex (VFC), and visual cortex) is specialised for behaviourally relevant, but invalidly cued targets, salient and unexpected stimuli (Corbetta and Shulman 2002, Vossel et al. 2014). Importantly, during visual search, high visual short-term memory load, and top-down guided attention this pathway is suppressed (Shulman et al. 2003, Todd et al. 2005). Re-activation occurs when salient non-targets carry contextually relevant information (Geng and Mangun 2011), a mechanism depending on dorsal-ventral interactions (DiQuattro and Geng 2011). In a dynamic causal modelling study, a TPJ to IFG to FEF pathway was identified for the translation of contextually relevant information into attention control, facilitating behaviour by interacting with the dorsal regions (DiQuattro and Geng 2011).

Application of attention systems to our paradigm

The experimental conditions determine the activated pathway in the dual stream attention network. The ventral bottom-up attention guiding system is the fundament of unconscious p(rep) modulation: stimuli were “invalidly cued”, i.e. contextual organisation was not made known to the participants (Vossel et al. 2014), and stimuli were contextually/behaviourally relevant (Corbetta and Shulman 2002). Following our hypothesis, spatial attention, as a condition for contextual modulation of RS and of the dorsal system (Larsson and Smith 2012, Vossel et al. 2014), demands a switch from the ventral to the dorsal attention system. The expertise with faces (Grotheer and Kovacs 2014) might reflect the behavioural relevance that is needed to alert the TPJ (Corbetta and Shulman 2002) as a key-region of the ventral attention network (Fig. XXV). It gives access to the ventral-dorsal-connecting pathway, via TPJ-IFG-FEF (DiQuattro and Geng 2011). Thus, contextual and behaviourally relevant information facilitate processing in the dorsal system (see Kveraga et al. (2007)). The suppression and reactivation of the ventral attentional system by interacting pathways (DiQuattro and Geng 2011) might be crucial for the “dynamic involvement of higher prediction areas” during p(rep) modulation. Higher-level predictions originate from frontal regions (locations being discussed below) and are transmitted to FFA, OFA and LO. Prediction of low-level value originates in the FFA and is transmitted to OFA, LO, early visual cortex (EVC) and the lateral geniculate nucleus (LGN) (Grotheer and Kovacs 2016). A novelty is the connecting TPJ module that is thought to be updated from frontal and sensory face processing regions attributing the necessity of process facilitation (Fig. XXV).

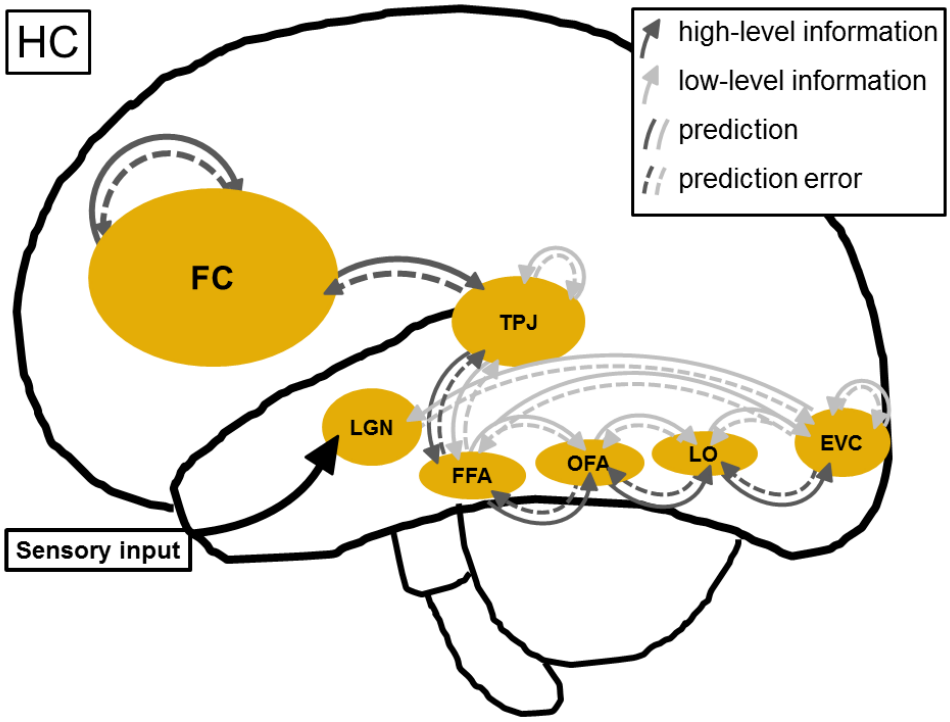

Figure XXV: Schematic illustration of the dynamic high-level involvement. The two stage model according to Grotheer and Kovacs (2016) (used with permission) is adapted for the p(rep) modulation paradigm as suggested in HC. The information of high-level value (depicted in dark grey) is processed in dependence to high-level prediction areas, whereas low-level information may be encoded in the low-level network (depicted in light grey). Novel, the TPJ as key-region that gives access to facilitating processes in dependence of contextual relevance of the stimuli. (LGN - lateral geniculate nucleus, EVC – early visual cortex, FFA – fusiform face area, OFA – occipital face area, LO –dorsocaudal part of the lateral occipital complex, TPJ – temporo-parietal junction, FC – fontal cortex)

Interestingly, in SZ the parvocellular stream was suggested to be rather intact, compared to probable disturbance in the magnocellular pathway (Butler et al. 2001, Foxe et al. 2005). Thus, the major role of ventral stream processing in p(rep) modulation of RS might be emphasised regarding the findings of the prediction of repetitions in both groups. Moreover, the TPJ is thought to play a key-role in the experimental condition of our paradigm demanding an attention-system-switch. Crucially, TPJ, STG, and IFG were found to be reduced in activity in context of implicit social functioning in SZ (Das et al. 2012). The strong interaction from TPJ to right STG is crucial for the identification of behaviourally relevant stimuli (Jou et al. 2010).

The role of identified regions in the p(rep) paradigm

As our whole-brain analysis of the SZ group showed several areas being activated (bilateral STG and transversal temporal area) compared to only left STG in HC, these might have a compensatory role for the TPJ deficits of SZ (Fig. XXVI) (Das et al. 2012, Wynn et al. 2015, Jimenez et al. 2016). The interaction with TPJ is likely because of the location of these neighbouring regions. The interaction of FFA, OFA, LO and STG signalling behavioural relevance might alert the TPJ and subsequent higher frontal or parietal regions of the dorsal attention network that encodes contextual predictions (IFG and FEF contextual decoding) (Corbetta and Shulman 2002, DiQuattro and Geng 2011).

The insula and parahippocampal gyrus activations were observed in the second-level analysis in SZ (shown in Fig. XXVI). Emotion and saliency processing is attributed to the insula (Terasawa et al. 2015). Insula activation is thought to maintain alertness to stimuli, comparable to the identified pre-stimulus network of the thalamus, anterior insula and ACC in an auditory detection task (Sadaghiani et al. 2009). The “pre-stimulus activity”, i.e. the brain’s activity prior to stimulus, might be in line with our above-described “stand to attention” hypothesis and facilitate perception (Qin et al. 2016). The parahippocampal gyrus is part of the MTL that is generally proposed to be involved in associative memory encoding (Pirnia et al. 2015). Behrendt (2013) suggested the hippocampus as a converging nexus for the ventral and dorsal visual stream with the function of integrating contextual information, such as the emotional/social information sent from the insula. Our interpretation is that the parahippocampal gyrus might attribute associative salience to faces, possibly in a compensatory manner. The area was found to be activated in SZ, but not in HC which is consistent with studies reporting hippocampal abnormalities related to memory functions (Heckers 2001).

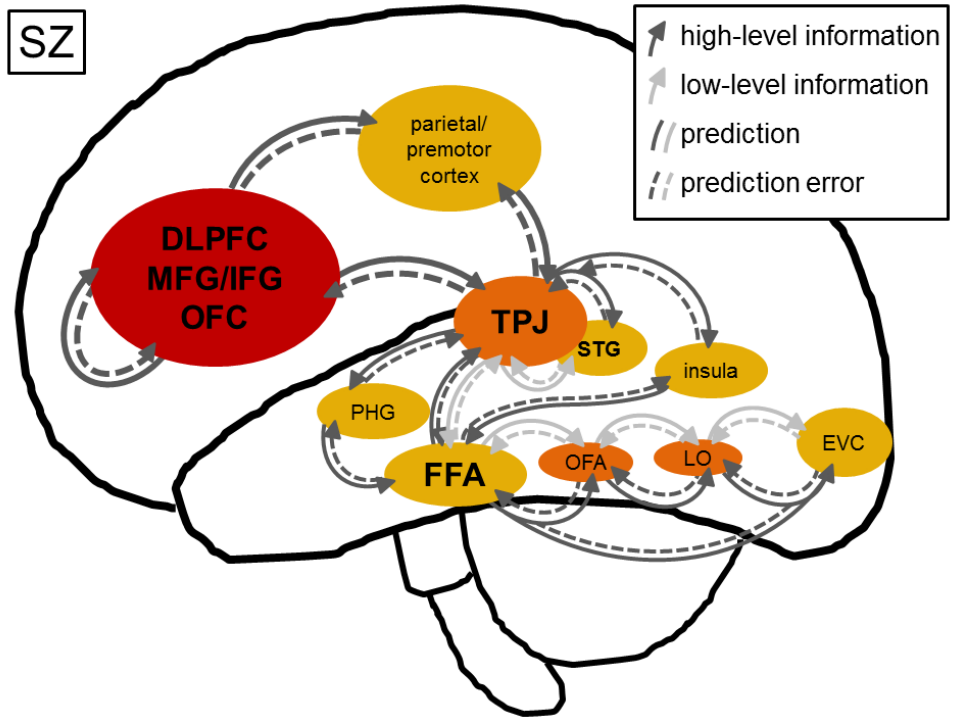

Figure XXVI: Schematic illustration of the dynamic high-level involvement in SZ. The two-stage model according to Grotheer and Kovacs (2016) (used with permission) is adapted for the p(rep) modulation paradigm tested in SZ. The information of high-level value (dark grey) are processed in high-level prediction areas when TPJ gives access to (see DiQuattro and Geng (2011), whereas less complex information may be encoded in the low-level network (light grey). In comparison to the "dynamic high-level involvement" in healthy participants, the disturbance in function (orange and red areas) are thought to be compensated by rather intact and strongly connected regions (yellow areas). Insula, PHG and STG integrate contextual information in alliance with FFA and TPJ. The deficits of OFA and LO can be balanced via a direct information exchange between FFA and EVC and frontal abnormalities in all of these possible top-down-regulating areas may be stabilised with parietal/ premotor cortex response. (EVC – early visual cortex, FFA – fusiform face area, OFA – occipital face area, LO –dorsocaudal part of the lateral occipital complex, TPJ – temporo-parietal junction, FC – fontal cortex, PHG – parahippocampal gyrus, DLPFC – dorsolateral prefrontal cortex, MFG - medial frontal gyrus, IFG - inferior frontal gyrus, OFC – orbitofrontal cortex)

HC exhibited additional activation in the lingual gyrus, which is situated in the infero-medial part of the occipital lobe and strongly connected with the neighbouring FG (Bogousslavsky et al. 1987). Dowlati et al. (2016) uncovered top-down connections from the middle temporal to lingual gyrus serving perceptual switch decisions utilised to control perceptual beliefs (perceptual change in ambiguous figures).

To enable an interaction of ventral and dorsal attention networks via the temporo-parietal junction (TPJ) (Kveraga et al. 2007, DiQuattro and Geng 2011), the known deficits in the dorsal visual system and TPJ in SZ (Foxe et al. 2005, Das et al. 2012)

are suggested to be compensated through involvement of the superior temporal gyrus (STG), insula and parahippocampal regions in SZ in our paradigm (FIG. XXVI).

5.5. Top-down control in the p(rep) paradigm

The influence of the dorsal attention network seems to be crucial in the processing of p(rep) modulation and the switching from ventral to dorsal system seems to enable the dynamic involvement of prediction areas. The “stand to attention” position of the high-level system requires a certain preserved function of high-level prediction regions and connections between the two-stages. Friston (2002) described schizophrenia explicitly as a functional dysconnectivity syndrome and more specifically prefrontotemporal connection deficits were reported in SZ by Friston and Frith (1995). A recent study of Klingner et al. (2014) showed functional connectivity alterations from brain areas to the thalamus during a resting state, such as superior temporal, fusiform, inferior frontal, insula and inferior occipital region (mentioning only the relevant areas for our experiment). Based on a literature synthesis, possible predicting areas involved in our paradigm and with regard to the dysconnectivity condition in SZ is presented: DLPFC, OFC, MFG, IFG, parietal and premotor region (Fig. XXVI).

The DLPFC was proposed as an area of interaction between the dorsal and the ventral system (van Polanen and Davare 2015), with the function of “information holding and manipulation” (Diamond 2013). Thus a necessary region in our paradigm, in contrast to the MMN-model with a simple storing mechanism relying on short term memory (Wacongne 2016). In SZ abnormalities of callosal fibres to the DLPFC were identified as characteristics of chronic stage (Wu et al. 2015).

The OFC as part of the extended face processing network (STS, amygdala, IFG) (Ishai 2008) is suggested to have potential as prediction source (Bar et al. 2006). Summerfield et al. (2006) proposed OFC (in addition to TPJ and MFG) to be a possible area for face template representation. More importantly, stimuli accessing the dorsal attention network are predicted in a top-down connection to ITG (Kveraga et al. 2007). OFC and temporal cortex demonstrated abnormal functional connectivity in early-onset SZ during resting state fMRI (Zheng et al. 2016). OFC gray matter volume is possibly dependent on the SZ positive/negative symptom dominance

(Zhang et al. 2015). Involvement of the OFC is highly probable in our paradigm and a likely source for compensation of dysconnectivity.

The MFG might be relevant as a supporting region to OFC since it participates in contextual information filtering (Poppe et al. 2016). Its high-level predictive role in face processing paradigms was suggested by Summerfield et al. (2006) and Grotheer and Kovacs (2015). Comparable to DLPFC, MFG was found to be a linking region between the dorsal and ventral attention systems (Corbetta et al. 2008, Fox et al. 2006). Also in PPI testing in SZ, MFG was attributed a major role (Hazlett 2001).

The IFG is thought to be part of the network connecting the dorsal and ventral stream, so that finally FEF might decode contextual information (DiQuattro and Geng 2011). It is assumed that both MFG and IFG respond to regularities in stimulus sequences (Vossel et al. 2011). But again, SZ showed reduced activation in IFG during an fMRI social functioning study (Das et al. 2012).

Moreover, parietal and premotor areas should be considered as interacting and compensatory regions (Fig. XXVI). Behrendt (2004) described an interaction of PFC and parietal cortex via premotor areas for passivity models to that our implicit paradigm might be belonging to, as well. Parieto-premotor interaction was proposed as a compensatory principle during unconscious prediction processing of corollary discharge (Murata et al. 2016) and during early face processing deficits in SZ (Quintana et al. 2001). Also, Grotheer and Kovacs (2016) suggested parietal BA7 involvement during ES, the conscious prediction processing in healthy participants.

In summary, it can be concluded that IFG and FEF (DiQuattro and Geng 2011), dorsal attention regions interacting with OFC and MFG, participate in predictions (Kveraga et al. 2007, Summerfield et al. 2006). The executive control region, DLPFC (Medalla and Barbas 2009, van Polanen and Davare 2015) and the interacting parietal region (Behrendt 2004, Santangelo 2015) might be involved in the p(rep) modulation, as well. An MEG study reported that contextual cue decoding requires stronger activation in FEF, DLPFC and VLPFC for correct performance, when SZ show increased error proneness (Manoach et al. 2013). In our paradigm showing a lack of group difference, it can be assumed that function of high-level regions was sufficient for intermittent involvement. Thus, activation was only necessary when experimental conditions, such as behavioural relevant stimuli giving contextual cues,

exceed the low-level system.

5.6. Limitations of the study and future distinctions

This experiment is not sufficient to determine the high-level processing areas involved in the p(rep) modulation in RS. All of the areas presented above are possibly influencing regions in the p(rep) modulation of RS for faces. Confounding factors for the activation levels are stage of the disease (Wu et al. 2015, Zhang et al. 2015, Zheng et al. 2016), task demands as mentalising task (Das et al. 2012) and the methods used (such as PPI (Hazlett et al. 1998), resting-state (Hoptman et al. 2010)). The comparison of several methods should expand our view on the findings on unconscious, visual prediction processing of salient stimuli. Comparison of different methods, such as ERP and fMRI is not trivial (Grill-Spector et al. 2006), but at the same time more informative for the analysis of the underlying mechanisms. Moreover, the compensatory impact of second-level analysis revealed areas and the prediction areas are suggested based on literature synthesis. This might be understood as the hypothetical approach to future research. A possible explanation for the discrepancy between the studies reporting prediction impairments and our present study might be that the ventral visual stream would be relatively intact, compared to the dorsal visual system (Javitt and Freedman 2015), the auditory (Todd et al. 2014) or somatosensory system (Shergill et al. 2014).

To prevent selection bias, a one-by-one matching between subjects in the two groups was implemented, based on age, gender and education, and the several clinical scores have been assessed: reviewing previous studies, for example the meta-analysis of Minzenberg et al. (2009) including studies varying in BPRS score from 16 to 56.6, our patient group BPRS (average score: 34.7±1.8) compared well within this range; this is also the case for SANS (7.3 to 63.9) and SAPS (9.8 to 27) (our SZ - SANS composite score: 36.7±3.9, SAPS composite score: 13.5±2.3). Moreover, in Bora et al. (2011) the age of the participants included in the studies varied from 21.4 to 50.9, and the duration of the disorder ranged from 0.8 to 21.8 years (our SZ – age: 34.6 ±2.2, time since diagnosis: 9.4±1.3 years). Wynn et al. (2015) indicated a CPZ equivalent of 307±153 mg/d (our SZ - CPZ equivalent: 318.7±69.3 mg/d). Thus, our group is in the range of study cohorts that is comparable to those of the literature. We acknowledge that the extrapolation of our data to the general SZ population is limited due to the number of subjects. However,

recent similar imaging studies of SZ reported a sample size ranging from 10 towards 25. Significant adaptation to faces was found with a sample size of n=10 (Bleich-Cohen et al. 2009), n=14 (Yoon et al. 2006), n= 17 (Habel et al. 2010), n=25 (Williams et al. 2013).

Subtypes of SZ are worth to mention looking at a relationship between cognitive abilities and cerebral structure when theoretically assuming that our participants reflect such a subgroup. In previous studies, subtypes were correlated to pattern of lingual gyrus and OFA, hippocampus and fronto-parietal brain regions according to cognitive outcome, such as verbal fluency, face memory, motor memory (Geisler et al. 2015). Additionally, symptom categories were correlated with gray matter reduction: highest reduction in positive symptom-group for ventromedial PFC, lingual, occipitotemporal region (Zhang et al. 2015). Paranoid patients differed from non-paranoid patients in the activation pattern of the social cognitive network (FFA, STS, amygdala, VLPFC) (Pinkham et al. 2008). These concerned regions are reflected in the Discussion as well.

Regarding antipsychotic medication, 15 of 17 patients received neuroleptic treatment at the time of testing. Here, the absence of substantial differences between groups suggested a lack of a negative systematic effect of medication on p(rep) prediction. This is in line with previous studies investigating structural and functional correlates of antipsychotics: gray matter volume reduction was not correlated with antipsychotic dose or duration of antipsychotic medication (Kuroki et al. 2006), and at the functional level, D2 or 5HT2 antagonists (such as Clozapine and Olanzapine) did not show any influence on mismatch signals (Csukly et al. 2013). It is important to note that there are studies reporting GABAergic and cholinergic effects on repetition priming (Thiel et al. 2001) and on repetition adaptivity (Stephenson et al. 2003). Silverstein et al. (2010) observed that cognitive abilities significantly improved during treatment due to the modulation of disrupted NMDAR–mediated synaptic plasticity by antipsychotics (Stephan et al. 2009).

Future studies should focus on functional connectivity to identify the cause for the preserved prediction in the p(rep) modulation of RS of neutrals faces in SZ. To our knowledge, the influence of dysconnectivity on unconscious prediction processing has not yet been investigated in more detail. Methods for assessing perceptual prediction, such as PPI, corollary discharge, MMN and p(rep) modulation of RS and

their underlying neuronal mechanisms should be investigated in parallel, with modelling studies to compare the tested cerebral function.

5.7. Conclusion

Building up a neural model about predictive modulation of RS might be key to understand unconscious processing of faces, not only under experimental conditions, but in an environmental setting as well. Assuming the model of independent RS and higher prediction processes (Grotheer and Kovacs 2016), this study revealed that prediction of face repetitions is based on about intact low-level function in SZ and HC. FFA was attributed a major role in processing as the area is capable to compensate for deficits, however depends on the basic functioning of early face processing regions. The effective compensation is suggested since RS phenomenon was shown in SZ in all face selective regions. Selective response to faces and the function of automatic processing of RS in SZ is interpreted as an ability to attribute salience to faces (see Downing et al. (2004)). This finding should be considered regarding the circuit of abnormal cognitive schemas including incorrect salience attribution that are thought to contribute to psychosis development in schizophrenia (Howes and Murray 2014). The parahippocampal gyrus might be associated with preserved salience processing of faces in SZ.

In consequence of preserved basic face processing and fulfilled RS effect, the prediction effect in SZ interestingly did not differ from HC in all areas investigated. The “dynamic high-level involvement” stipulates an interaction of the initially activated ventral stream and the higher prediction dorsal pathway. The face stimulus as social stimulus, with the need of high expertise, was crucial for the switch of attention systems and facilitation of stimulus processing. Possibly compensatory regions were identified in the whole-brain analysis in SZ. Thus, prediction of repetition likelihood and associative salience to faces are mechanisms that were thought to balance dysconnectivity and regional function deficits in schizophrenia. The role of the ventral visual stream processing, being rather intact, was emphasised.

The analysis of underlying neural mechanisms for the typical paradigms of MMN, PPI and corollary discharge experiments helped to attribute validity as methods investigating prediction. All of these methods indicated disrupted ‘gain control’, thus deficits in prediction. However, it is probable that local disturbance of stimuli

processing, such as in the auditory system (Javitt and Sweet 2015), has a relevant influence on disrupted processing of the tested paradigms, and additionally high-level involvement is not evident for MMN (Wacongne 2016) and PPI (Hazlett and Buchsbaum 2001). The comparison of these methods is useful in identifying compensatory mechanisms in schizophrenia, as the involvement of parietal or premotor regions for social cognitive function (Murata et al. 2016). It can be considered as novel that SZ show a preserved automatic processing of faces in the local level, and that high-level involvement can be established when the network of sensory and prediction areas allows a relative compensation of function.

The abnormal assignment of environmental experiences is thought to provoke abnormal perceptual beliefs in schizophrenia (Kapur 2003), but our study revealed that unconscious recognising of contextual modulation of faces is preserved. As the basic function of neutral face prediction showed no difference in comparison to HC, a crucial part of the environmental stimuli is much better encoded than expected, based on the social cognition literature (Hall et al. 2004, Csukly et al. 2013, Howes and Murray 2014). Therefore, this study essentially progresses the research on perceptual function in schizophrenia.

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Wissenschaftliche Veröffentlichung

Die Ergebnisse dieser Studie wurden zur Veröffentlichung eingereicht.

Manuskript: „Significant repetition probability effects in Schizophrenia“

Autoren: Prof. Gyula Kovács, DSc; Dr. Mareike Grotheer; Lisa Münke;

Prof. Szabolcs Kéri; PD Igor Nenadić

Abstract:

A growing body of evidences suggests that the comparison of expected and incoming sensory stimuli (the prediction error (ε) processing) is impaired in schizophrenia patients (SZ). For example in studies of mismatch negativity, an ERP component that signals ε, SZ patients show deficits in the auditory and visual modalities. To test the role of impaired ε processing further in SZ, using neuroimaging methods, we applied repetition suppression (RS) paradigm. Patients diagnosed with SZ (n=17) as well as age and gender matched healthy control subjects (HC, n=17) were presented with pairs of faces, which could either repeat or alternate. Additionally, the likelihood of repetition/alternation trials was modulated in individual blocks of fMRI recordings, testing the effects of repetition probability (P(rep)) on RS. We found a significant RS in the fusiform and occipital face areas, as well as in the lateral occipital cortex that was similar in patients of SZ. More importantly, we observed similar P(rep) effects (larger RS in blocks with high frequency of repetitions than in blocks with low repetition likelihood) in the patient group as well. Crucially, this suggests that prediction effects, elicited by stimulation probability modulations affect the neural responses in schizophrenia as well.

Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass mir die Promotionsordnung der Medizinischen Fakultät der Friedrich-Schiller-Universität bekannt ist,

ich die Dissertation selbst angefertigt habe und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben sind,

mich folgende Personen bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskripts unterstützt haben:

PD Dr. Igor Nenadić,

Prof. Gyula Kovács,

Dr. Mareike Grotheer,

Dr. Géza Ambrus,

die Hilfe eines Promotionsberaters nicht in Anspruch genommen wurde und dass Dritte weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen,

dass ich die Dissertation noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht habe und dass ich die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung nicht bei einer anderen Hochschule als Dissertation eingereicht habe.

_____ _____

Ort, Datum Unterschrift

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