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DISSERTATION

Neurophysiology of face processing: Extending the functional significance of event-related potentials in lateralization, adaptation, and prediction processes

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Abstract

English

Linking event-related potentials (ERPs) to relating, underlying processes that create accurate face representations and to their generating sources is a very complex matter that has to take into account multiple factors such as characteristics of the subject, stimuli characteristics and other processes within the hierarchal predictive network of the brain. While the physical features of ERPs are well established in literature today, the exact stages in the analysis of face stimuli that they reflect and their clinical implications still remain insufficiently understood. The aim of the present dissertation was to expand the functional significance of mid-latency components of the visual ERP associated with face processing by applying novel paradigms in order to contribute to linking these factors. Study 1 examined the hemispheric lateralization of the N170 by using a tachistoscopic presentation paradigm and found evidence for differential functional lateralization in face processing in females and males. Study 2 then further investigated the N170 by employing repetitions of identical and non-identical faces, as well as parametrically varied interstimulus intervals. Study 2 thereby demonstrated an encoding of face identity by the N170, which is mirrored in the duration of the N170 adaptation and also ruled out confounding effects by low-level adaptation. Lastly, Study 3 translated prior findings of a facilitated cortical prediction error response into a clinical sample by providing evidence of a strongly reduced visual mismatch negativity in schizophrenia compared to healthy subjects, but no such difference in trials with emotional stimulus context. Study 3 in that way also helped to characterize coding of facial affect in more depth. In all three studies, the ERP components of interest were shown to have an even wider relevance within the concepts of lateralization, adaptation and prediction processes than stated in earlier studies. The advantages of combining the described methodological approaches on a theoretical and practical level are discussed. In addition, all three studies contribute to and support the hierarchical predictive coding model.

Deutsch

Ereigniskorrelierte Potentiale (EKP) zu verknüpfen mit zugrunde liegenden Prozessen, die eine akkurate Gesichtsrepräsentation ermöglichen, sowie zu den erzeugenden Quellen ist ein sehr komplexes Unterfangen, welches viele Faktoren berücksichtigen sollte, so zum Beispiel Eigenschaften des Beobachters, Eigenschaften des Objektes und weitere Prozesse innerhalb des hierarchisch prädiktiven Netzwerkes des Gehirns. Während die physikalischen Eigenschaften von EKPs weitestgehend beschrieben sind in der heutigen Literatur, so bleiben die genauen Stufen in der Analyse von Gesichterstimuli, welche sie repräsentieren und die klinischen

Implikationen unzureichend verstanden. Das Ziel der vorliegenden Dissertation war es, die funktionale Signifikanz von mittellatenten Komponenten des visuellen EKP zu erweitern, indem neue Paradigmen angewendet werden, um somit einen Beitrag zu leisten diese Faktoren in Zusammenhang zu bringen. Studie 1 untersuchte die hemisphärische Lateralisierung der N170 unter Nutzung eines tachistoskopischen Darbietungsparadigmas und fand Hinweise für eine unterschiedliche funktionale Lateralisierung in der Gesichterverarbeitung zwischen Frauen und Männern. Studie 2 untersuchte ebenfalls die N170 unter Nutzung von wiederholten Darbietungen von identischen und unterschiedlichen Gesichtern mit parametrisch variierten Interstimulusintervallen. Studie 2 hat dadurch die Enkodierung von Gesichteridentität demonstriert, welche sich in der Dauer der Adaptation der N170 widerspiegelt, auch wurden konfundierende Effekte von niedrigschwelliger Adaptation ausgeschlossen. Zuletzt überführte Studie 3 frühere Ergebnisse einer erleichterten kortikalen Vorhersagefehlerreaktion in eine klinische Stichprobe und ergab Hinweise auf eine deutlich reduzierte visuelle Mismatch-Negativität bei schizophrenen Patienten verglichen mit gesunden Kontrollprobanden, jedoch ohne diesen Unterschied in Versuchsteilen mit emotionalem Kontext zu finden. Studie 3 hat auf diese Weise geholfen die Kodierung von, im Gesicht gezeigten, Emotionen weitergehend zu charakterisieren. In allen drei Studien konnte gezeigt werden, dass die EKP Komponenten von Interesse eine noch größere Relevanz haben in den Konzepten Lateralisierung, Adaptation und Vorhersageprozessen als es in früheren Studien angenommen wurde. Die Vorteile einer Kombination der beschriebenen methodischen Zugänge für Theorie und Praxis werden diskutiert. Zudem haben alle drei Studien die Annahmen des hierarchisch prädiktive Kodierungsmodells bestätigt.

Preface

The dissertation is based on three prior conducted and published studies (declaration of contribution is described in detail for all three studies on page 30). Parts of the paragraphs within the introduction, methods, results and discussion section are revised or cited work from these articles.

1 Introduction

1.1 Studying face processing by means of neurophysiology

Correctly recognizing and identifying another person's face is one of the core abilities of social functioning. Faces hold a broad variety of socially relevant information about an individual, such as sex, age, attractiveness, behavioral intent, identity or expressed emotion, which makes accurate face recognition essential for social interactions[1]. Humans are incredibly fast (producing an internal image of a face is accomplished within 200 ms after stimulus presentation)[2,3] and accurate at processing faces, which is remarkable given that faces are highly complex visual patterns. Due to its high temporal resolution, the electroencephalogram (EEG) is well suited for investigating the cognitive operations and neuronal signatures associated with the processing of faces. The wide application of EEG in face processing research is for example reflected in a PubMed query (22nd October 2018) which revealed 1,262 scientific articles when searching for "face processing" and "EEG". Expanding the knowledge of functional significance of event-related potentials (ERPs) in face processing by employing novel paradigms and thereby expanding the literature on underlying operations is the aim of this dissertation. In face processing, the N170 is one of the most commonly investigated ERP and is usually evoked by the appearance of a face stimulus. The N170 is a negativity measured at occipito-temporal electrodes that typically occurs at 150-200 ms after stimulus presentation and is significantly larger in response to faces than to other objects.[2,4,5] The N170 seems to be primarily generated from sources located around the posterior portion of the inferotemporal lobe.[6-10] While these physical dimensions are well established in literature today, the exact stages in the analysis of a face that the N170 and other ERPs (e.g. later processes such as the visual mismatch negativity (vMMN)[11-13]) reflect still remain insufficiently understood. For the N170 for example it was often stated that it reflects a stage of pre-categorical structural encoding[2], since it is not directly affected by familiarity of a face[4]. However, this dissertation will provide evidence that linking ERPs and underlying stages of face processing is a very complex matter that has to take into account multiple factors such as lateralization, amplitude, temporal decay, stimuli characteristics (e.g. affect, size), sex of the viewer, top-down and bottom-up processes to name only a few. For that purpose new paradigms will be applied in this dissertation in order to more specifically investigate the role of these factors in ERPs associated with face processing. This dissertation aims at expanding the functional significance of mid-latency components of the visual ERP associated with face processing by employing novel paradigms in the following aspects:

- The N170 ERP component will be examined in terms of its hemispheric lateralization and potential sex differences in order to contribute to a long-standing discussion on N170 lateralization, which may fundamentally confound study results on face processing. For that purpose, a tachistoscopic hemifield paradigm employing famous and unfamiliar face stimuli will be put to work, for the first time in combination with EEG analysis to elucidate that basic matter of face representation.
- The encoding of face identity will be addressed using a temporally graded adaptation paradigm to determine the relative contribution of the N170 to encoding face identity.
- The impact of affective valence on the vMMN will be addressed in a clinical sample by using an emotional sequence oddball paradigm to estimate differential responsivities of cortical information processing cascades to a most important social cue, i.e. a face's emotional context.

1.1.1 Investigating the sensitivity of N170 to hemisphere and sex using a tachistoscopic hemifield paradigm

As described by Stasch and colleagues[14], earlier studies have consistently found a right-hemispheric (RH) dominance for face processing.[15-18] On the contrary, more recent studies point to a substantial left-hemispheric (LH) involvement in face recognition,[19,20] especially those employing neuroimaging,[21-24] thereby emphasizing a bi-hemispheric involvement and dimensional view on hemispheric specialization. Interhemispheric cooperation during visual processing can be studied by comparing unilateral with bilateral presentation of identical stimuli.[25,26] Using this paradigm, several studies replicated a RH advantage (with a LH contribution) for faces, but also found a bilateral advantage and evidence for interhemispheric cooperation during face processing.[27,28] Recent studies on hemispheric lateralization and interhemispheric interaction in face processing provide increasing evidence that sex differences might account for some of the heterogeneous data.[29-31] Studies employing face processing tasks provide evidence for a more pronounced functional lateralization in men compared to women.[32,33] Also, ERP studies indicated a more asymmetric functioning of the visual cortex during face encoding in men, whereas women display a more bilateral brain activation pattern.[34-37] In order to elucidate the raised issues, study 1 employs a lateralized tachistoscopic hemifield paradigm using face stimuli and therefore enables the investigation of hemispheric interaction in face processing. More importantly, by applying this experimental design to both female and male subjects evidence could be retrieved that might help to disentangle the so far inconclusive data on hemispheric specialization in face processing.

1.1.2 Investigating the sensitivity of N170 to face identity using a temporally graded adaptation paradigm

Beyond the scope of interhemispheric interaction and sex differences, the N170 is furthermore under investigation for other aspects of face recognition such as its sensitivity to face identity. The N170 and other ERPs, such as the N250[38] or the N250r[39], have received special attention in exploring the temporal dimensions of the different processes underlying the perception of identity. Studies comparing different types of stimuli found that the N170 is not altered by familiarity of a face per se.[4] Bentin and colleagues[2] suggested that the N170 is probably connected to a face-specific structural encoding mechanism that is not directly involved in the identification of faces. However, more recent studies have challenged that hypothesis repeatedly by employing repetition suppression (RS), or adaptation paradigms. Adaptation is referred to as an attenuated neuronal response following the repeated exposure to identical stimuli, thereby suggesting neuronal sensitivity to these stimuli (see Grill-Spector and colleagues[40] for a review). As described by Shen and colleagues[41], in face processing, the employment of RS paradigms to face identity encoding on the level of the N170 has led to contradictory results: while some studies demonstrated adaptation of the N170 amplitude in response to repeated presentations of identical faces,[42-48] other studies found no such effect.[49-53] Sorting these seemingly contradictory results suggests that positive reports were acquired with short to intermediate interstimulus intervals (ISIs), while negative results were based on intermediate to long ISIs. Other studies that employed non-identical faces and investigated the effect of different ISIs on N170 amplitude however consistently found significant adaptation effects only for short ISIs.[54,55] In study 2 this striking dissociation is under investigation by systematically varying ISIs in the context of face identity encoding.

1.1.3 Investigating visual mismatch negativity and its significance for facial affect coding in a clinical sample using an emotional sequence oddball paradigm

After reviewing literature on face representation and face identification and therefore on the spatio-temporal dimensions of the N170 the dissertation is now turning to another important aspect of face recognition, i.e. coding of facial affect and its underlying processes. Mismatch negativity (MMN) is an ERP response that directly follows the N170. In the visual modality, the vMMN occurs approximately at around 300 ms after stimulus appearance over posterior cortex areas.[56,57] However, this response only occurs if the stimulus differs from prior stimuli.[58] The MMN response is computed by subtracting the response to standard stimuli from the response to deviant stimuli. Therefore, it is thought of as a direct representation of the residual variance between higher cortical predictions (top-down) and sensory input (bottom-up), which is the prediction error[58]. For an overview of the hierarchical predictive coding framework[59-61] see figure 1.

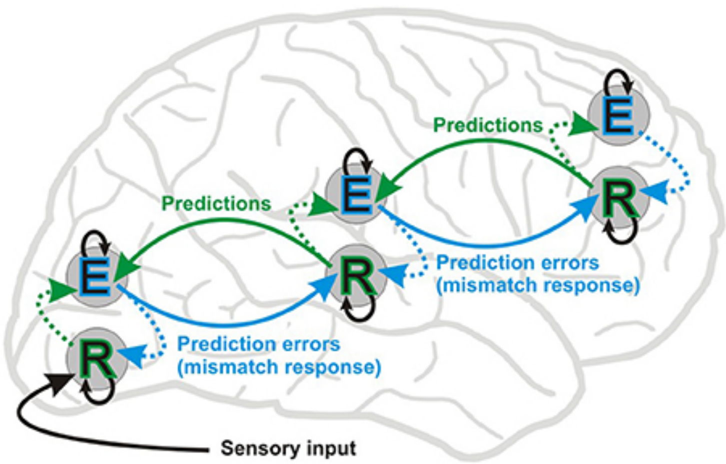

Figure 1. Simplified scheme of the hierarchical predictive coding framework.[59,61] The figure has been published first by Stefanics and colleagues.[60] Permission for using the figure in this dissertation has been kindly provided by the first author. The figure shows message passing between two putative neuronal populations: error units (E) and representation units (R). In this framework, bottom-up forward connections convey prediction errors (MMN or mismatch response) and top-down backward connections carry predictions, which explain away prediction errors (repetition suppression).

As described by Vogel and colleagues[63], based on these assumptions Zhao and Li[64] found a phenomenon they called expression-related mismatch negativity (eMMN). EMMN in their study was evoked by deviant happy and sad faces following a neutral face expression in a classic oddball paradigm. These findings have been replicated using more sophisticated techniques in the last years.[11,56,65,66] Interestingly, evidence from a recent study[67] employing a sequence oddball task even points to a facilitation of prediction error computation by emotional processing. That is, eMMN in that study developed about 100 ms earlier with a significantly pronounced amplitude compared with MMNs evoked by sequence deviants with a neutral expression. Prediction errors do not only provide information about the typical functioning of the brain while processing sensory input such as facial affect. They also provide a suitable framework to potentially contribute to the question why neurocognitive processes are impaired in some psychiatric disorders such as for example schizophrenia.[68] As coded by the ICD-10[69] psychopathological phenomena of schizophrenia can include for example thought echo, thought insertion or withdrawal, delusional perception, hallucinatory voices commenting or discussing the patient in the third person and negative symptoms. As described further by Vogel and colleagues[63], predictive coding deficits in patients with schizophrenia have been linked to many deficits e.g. reward and salience processing deficits[71] and repetition suppression deficits.[72] Study 3 therefore addresses the spatio-temporal dynamics of processing facial affect in healthy subjects and subjects with schizophrenia within the framework of predictive coding. This will contribute not only to a better characterization of facial affect coding, but also translate the predictive coding approach to facial affect coding into a clinical context.

1.2 Research questions

The following research questions are derived from the review of the current literature above.

Study 1: Are there differences in functional lateralization in males and females as measured by the N170?

The aim of study 1 was to identify potential differences in functional lateralization in males and females, which might account for the heterogonous findings in the literature. Furthermore, by employing unfamiliar and familiar face stimuli, the study furthermore aimed at identifying neurophysiological correlates of hemispheric differences in processing these two types of stimuli.

Study 2: Are there differential time courses of N170 adaptation to non-identical and identical face repetition?

By systematically investigating the effect of different ISIs on the N170 using identical and non-identical face stimuli, study 2 aimed at finding evidence for differential time courses of N170 adaptation to non-identical and identical face repetitions. The study also aimed at controlling for low-level sensory input via a supplementary experiment.

Study 3: What impact does emotion have on vMMN as a prediction error correlate in schizophrenia patients compared to healthy controls?

By employing a facial affect, i.e. emotional sequence oddball paradigm in healthy controls and subjects with schizophrenia, study 3 aimed at characterizing the coding of facial affect and providing insight into the magnitude of vMMN deficits in schizophrenia.

2 Methods

2.1 Study 1: Disentangling the interaction of sex differences and hemispheric specialization

Participants: Fifty-four healthy (no history of neurological or psychiatric disorder, normal verbal and non-verbal IQ, normal or corrected-to-normal vision), right-handed volunteers (27 females, 27 males) were financially compensated to participate in this study. Data sets from seven subjects who responded with accuracy levels close to chance were excluded from the final analysis, thus leaving a sample of 47 participants (24 females, 23 males). Male and female subjects were matched with regard to their verbal[73] and non-verbal IQs[74], Digital Symbol Test performances[75] and laterality quotients[76] (for a complete list of all questionnaires please refer to Stasch and colleagues[14]). Participants from all three studies included in this dissertation gave informed consent prior to the study, and all experiments were performed in accordance with the ethical standards of the Declaration of Helsinki. All three studies were approved by the ethics committee of the Charité - University Medical Centre Berlin, Germany.

Paradigm: Figure 2 gives an overview of the task.

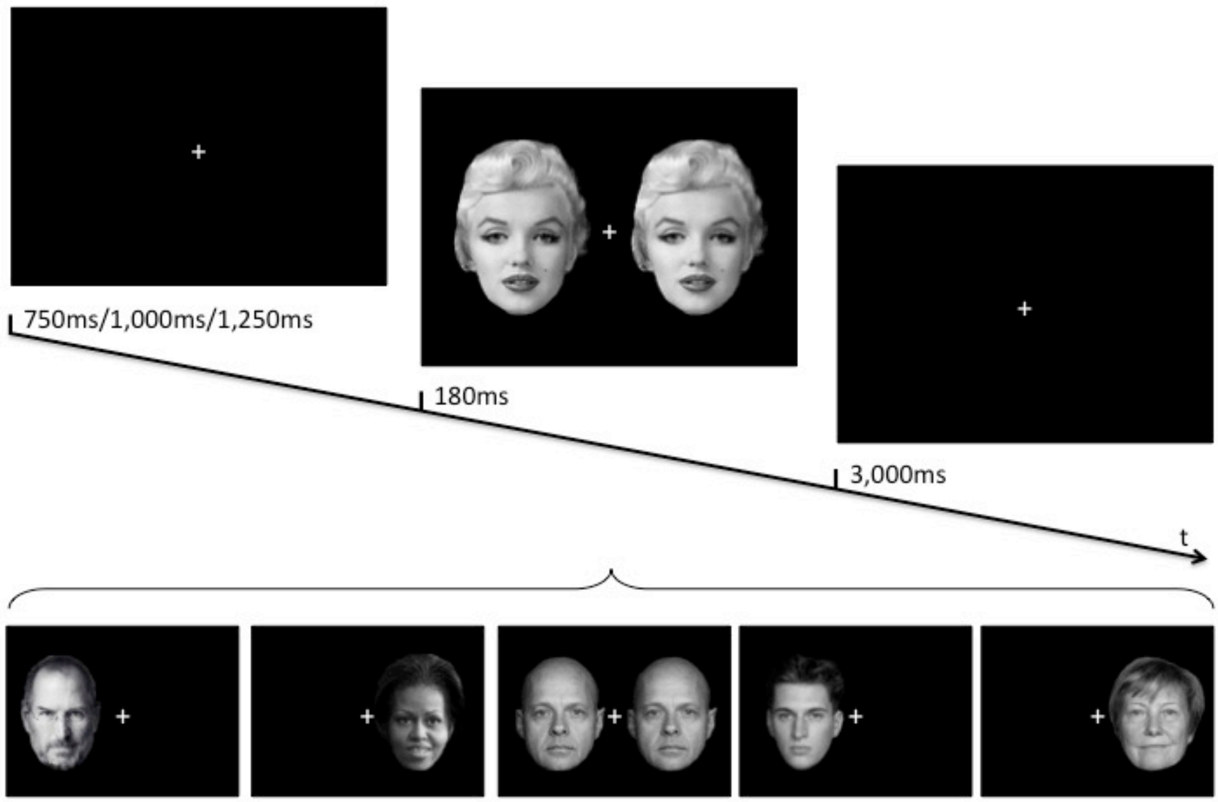

Figure 2. Paradigm of study 1. On screen instructions and an initial practice session preceded the experiment. At the beginning of each trial, a central white fixation cross appeared for 750 ms, 1000 ms, or 1250 ms creating

pseudo-randomly varying inter stimulus intervals. Then, a famous or an unfamiliar face (113 × 144 pixels) was presented in a lateralized tachistoscopic fashion either unilaterally to the left visual field, the right visual field, or bilaterally (lateral eccentricity of 4.5°) for 180 ms, followed by a black screen that appeared for 3000 ms. Participants were instructed to decide as quickly and accurately as possible whether the presented face was famous or unfamiliar. Responses were scored as correct if the correct key was pressed within a time window from 100 ms to 1800 ms after the target face was presented. A total of 300 trials were presented. Throughout the experiment, short breaks were allowed after every 60 trials.

Event-related potentials: EEG data was segmented to a length of 4500 ms for each experimental condition and corrected relative to a baseline from 100 ms to 0 ms before stimulus onset. After automated removal of artifact-contaminated epochs, averages were constructed for each experimental condition. The N170 component was determined as peak amplitude in the time window 150–190 ms post-stimulus presentation, based on a grand means across conditions. Electrode selection was based on the corresponding topographical map that led to selection of electrodes P7, PO7, PO9 and P8, PO8, PO10 for the analysis. Electrodes were pooled per hemisphere to avoid potential double dipping by post hoc electrode selection.[77] For an in-depth description of the EEG data acquisition and offline analysis with Brain Vision Analyzer 2.03 (Brain Products, Munich, Germany) please refer to Stasch and colleagues.[14]

Statistical analysis: Statistical analysis was performed with SPSS 19.0 or higher in all three studies (IBM, Armonk, NY). Behavioral data and EEG data were submitted to repeated measures analyses of variance (ANOVAs). ANOVA of the N170 included the within-subject factors Hemisphere (left versus right), Familiarity (famous versus unfamiliar faces), and Visual Field (LVF versus BVF versus RVF) and used Sex (female vs male) as a between-subject factor. Where appropriate, epsilon corrections were performed for heterogeneity of co-variances with the Huynh-Feldt method for the behavioral data and Greenhouse Geisser corrections for EEG data. Post hoc t-tests for paired samples were calculated for all significant main effects and interactions, as required. Bonferroni-corrections were applied to all post hoc tests. Alpha level was set at $p < .05$ for all tests.

2.2 Study 2: The encoding of face identity in the duration of N170 adaptation

Participants: Twenty-seven right-handed subjects (15 females, 12 males) participated in this study and were financially compensated. All participants were healthy as indicated by the same questionnaires already used in study 1.

Paradigm: Participants were instructed to observe photographs of unfamiliar female and male faces with neutral face expression and to respond to a target face by pressing a button as quickly as possible. Figure 3 gives an overview of the task.

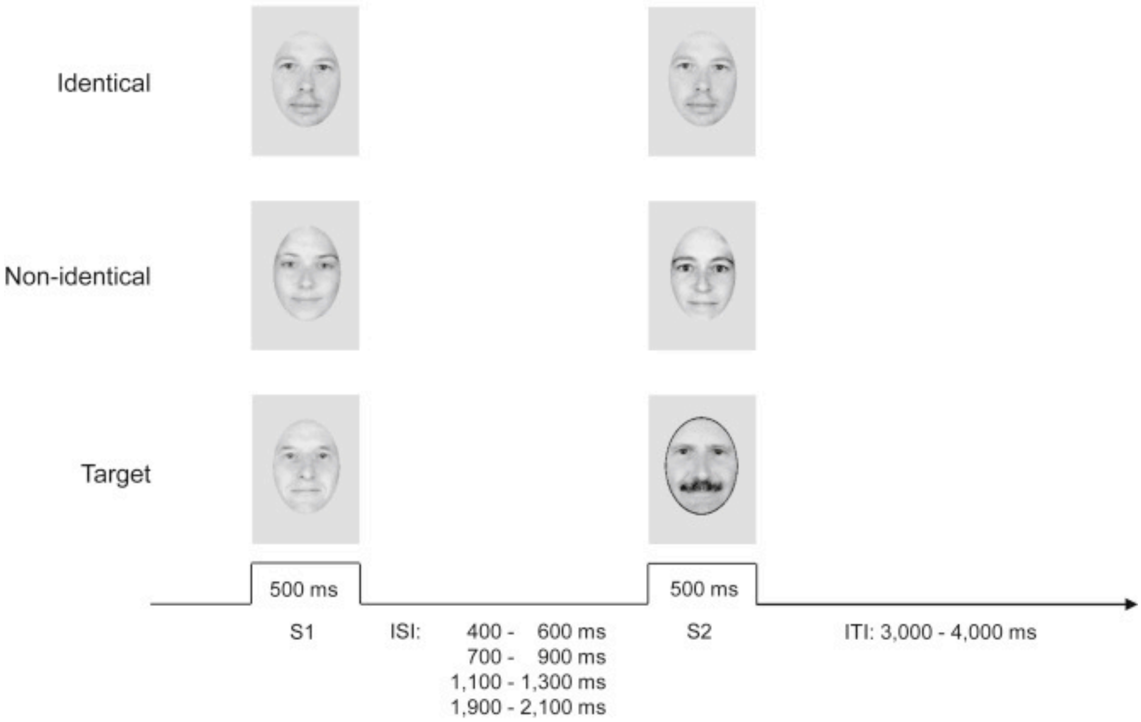

Figure 3. Paradigm of study 2. The figure has been published first by Shen and colleagues[41]. Stimuli were always presented for 500 ms and organized in pairs (S1, adapter stimulus; S2, test stimulus) with jittered interstimulus intervals (ISIs) of 400-600 ms; 700-900 ms; 1100-1300 ms; or 1900-2100 ms evenly distributed across blocks. Stimulus pairs showed either identical or different faces. Male and female faces were presented with a probability of .5 across the paradigm; in different face trials, either two different female or two different male faces were displayed. Target stimuli consisted of a cropped face with a black oval contour and facial hair. Target trials (p = .1) were evenly distributed across identical and non-identical trials. Inter-trial intervals (ITI) pseudo-randomly varied from 3000 to 4000 ms. A black fixation cross was visible in the center of the screen in the absence of a stimulus. Five blocks, each consisting of 60 stimulus pairs, were presented.

Event-related potentials: For an in-depth description of the EEG data acquisition and offline analysis with Brain Vision Analyzer 2.03 (Brain Products, Munich, Germany) please refer to Shen and colleagues.[41] EEG data was segmented to a length of 1000 ms for each experimental condition (S1 and S2, stimulus repetition, ISI) and corrected relative to a baseline of 100 ms directly preceding stimulus onset. Averages were then calculated for each experimental condition. The N170 was identified by assessing the latency of the maximum peak and estimating a time window using a butterfly plot of all averaged adapter stimuli and by using a corresponding topographical map to facilitate electrode selection. The N170 was scored at P7, P8 and TP7, TP8 as the most negative peak within 60 ms around the mean corresponding peak of the grand average (150-210 ms after S1/S2 onset). As in study 1, attention was given to the 'double dipping' rationale.[77]

Statistical analysis: Repeated measures ANOVAs of N170 amplitudes were performed and included the within-subjects factors Stimuli (S1 vs S2), Identity (identical vs non-identical) and ISI (400-600 ms vs 700-900 ms vs 1100-1300 ms vs 1900-2100 ms). Mauchly's test ascertained that the sphericity assumption was not violated. Post hoc t-tests for paired samples were calculated for significant main effects and interactions and included Bonferroni-corrections by multiplying the p-value with the number of post hoc comparisons. Alpha was set at $p < .05$ for all tests.

2.3 Study 2.1: Low-level sensory contributions to N170 adaptation

In a second experiment, retinal contributions to the N170 adaptation to face identity were under investigation. If not mentioned otherwise, the same experimental procedures as in study 2 were applied. Twelve healthy participants who have not been tested before (9 females, 3 males) performed an experiment in which the same face stimuli were used but two different stimulus sizes were employed (subtended visual angles of approximately 24 x 12° and 18 x 9°). As described by Shen and colleagues[41], identical or non-identical stimulus pairs were presented in either equal ($p = .5$) or different ($p = .5$) sizes in an orthogonal design, i.e., equally distributed trials with small/ large, large/small, small/small, and large/large faces as S1 and S2 stimuli, respectively. In total, 120 trials including target trials ($p = .1$) were presented pseudo randomly, each trial included S1 and S2 with stimulus duration of 500 ms and an ISI of 400-600 ms or 1100-1300 ms. The N170 was scored as the most negative peak between 130 and 210 ms at electrodes P7, P8 and PO9, PO10 and then pooled across all electrodes. A repeated measures ANOVA was performed.

2.4 Study 3: Emotional context in prediction error responses in schizophrenia

Participants: Seventeen patients diagnosed with schizophrenia (3 females, 14 males) and eighteen controls (3 females, 15 males) were paid to participate in this study. The two groups were matched for sex and age (±2 years). Due to technical artifacts one patient was excluded from the sample. All patients met DSM-IV criteria for schizophrenia and had no comorbid psychiatric disorder except for nicotine dependence. Other exclusion criteria were current illicit drug abuse, a history of severe neurological or medical disorder, and age below 18 or above 65 years. Symptom severity was assessed using the Positive And Negative Syndrome Scale

(PANSS).[78] As in study 1 and 2 the exclusion criteria mentioned above and any history of psychiatric disorders and/or a family history of psychiatric illness were applied to control subjects.

Paradigm: Participants observed the stimuli appearing on the screen while listening to a tale via headphones. Whenever they saw a face with a large and salient red star on it they had to press the mouse button (p=.1). Figure 4 gives an overview of the task.

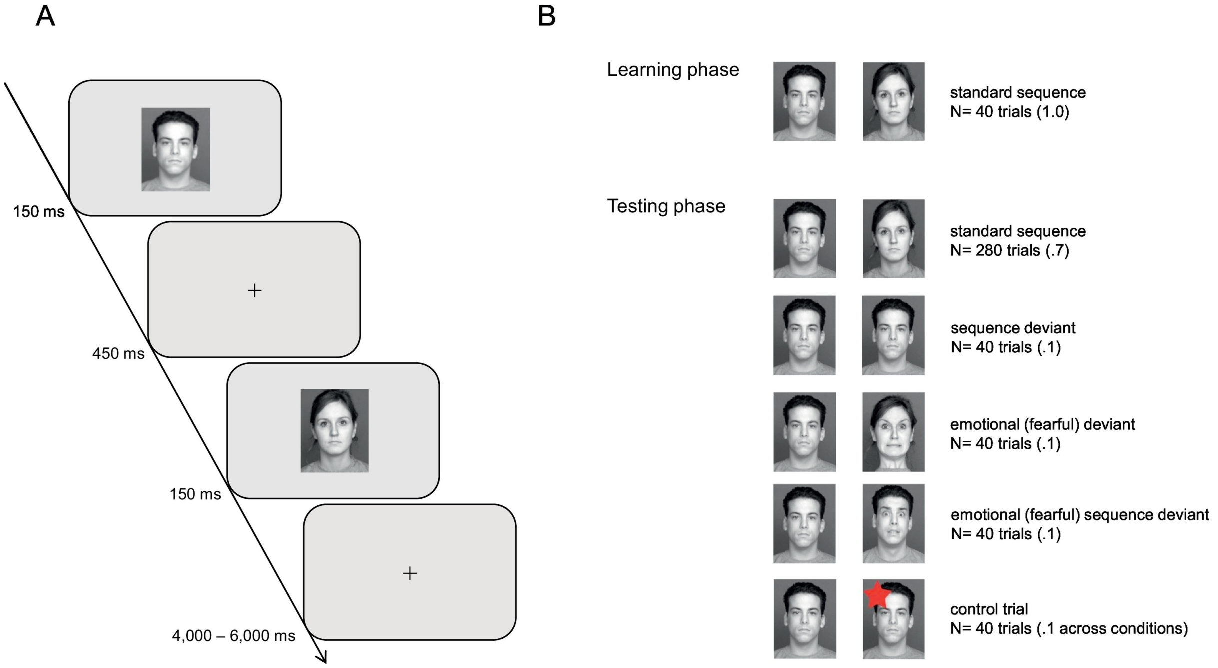

Figure 4. Paradigm of study 3. The figure has been published first by Vogel and colleagues.[63] The experiment consisted of a learning phase and a testing phase. During the learning phase, participants observed 40 repetitions of the standard sequence that consisted of a neutral male face followed by a neutral female face with a stimulus onset asynchrony of 600 ms and a stimulus presentation time of 150 ms. The aim of the learning phase was to establish this sequence as a top-down prediction so that any violations to this standard sequence would results in a prediction error in the following test phase. During the test phase, the same sequence served as the standard condition and was shown in 70% of all trials (N = 280). The deviant conditions consisted of a sequence deviant, an emotional deviant, and a sequence emotional deviant, each of which was presented in 10% of all trials (N = 40 each) during the test phase. Control trials for behavioral analysis of response accuracy (10% of all trials) were evenly distributed across all blocks. The conditions were pseudo-randomized across all 400 test trials. Every 100 trials, the participants were given a short break.

Event-related potentials: As described in detail by Vogel and colleagues[63], EEG data was segmented according to experimental conditions. After baseline correction, ERPs were averaged for each experimental condition, separately for each individual. At this point, the presence of a significant negativity in the deviant conditions compared with the standard condition was confirmed by extracting mean amplitude values. After that the ERP in response to the neutral standard was subtracted from the ERP in response to the three deviant conditions. The resulting difference waveforms contained different vMMN components, depending on the respective experimental condition: vMMN elicited by sequence deviants; vMMN elicited by emotional sequence deviants; and vMMN elicited by emotional deviants (eMMN). For these three components, six electrodes were selected that represent the underlying regions of interest: P7, P07, P09 (left hemisphere) and P8, P08, P010 (right hemisphere). Electrode selection was based on own previous research[57,67], and confirmed by topographical maps of the present data set. Peak detection of vMMN components evoked by sequence deviants was performed in the interval of 200–400 ms, and for eMMN components, i.e. evoked by emotional deviants and emotional sequence deviants, were scored at 150–300 ms. These intervals were selected based on previous research showing that emotional deviants elicited substantially earlier MMN components.[67]

Statistical analysis: In a first step electrodes of interest within each hemisphere were averaged for all MMN components to avoid circular analyses.[77] Then the ERP components were analyzed with repeated measures ANOVAs. In a first step, an ANOVA using the within-subject factors Condition (vMMN elicited by sequence deviants vs vMMN elicited by emotional sequence deviants vs vMMN elicited by emotional deviants (eMMN)) and Hemisphere (left versus right) and the between-subject factor Group (patients vs control subjects) was performed. In a second step, for the analysis of voltage and latency the factor Hemisphere was removed from analysis since it did not contribute to any main effects or interactions. Post hoc, significant main effects were analyzed using pairwise comparisons and independent samples t-tests; all post hoc tests were corrected using the Bonferroni-method. Alpha was set at $p < 0.05$ for all tests.

3 Results

3.1 Study 1: Disentangling the interaction of sex differences and hemispheric specialization

N170 amplitudes: As described by Stasch and colleagues[14], an omnibus ANOVA revealed a significant main effect of Visual Field based on a significantly larger amplitude in the BVF compared to the LVF and the RVF condition. The interaction of Hemisphere x Visual Field was driven by larger amplitudes in the hemisphere contralateral to stimulation, as shown by pairwise Bonferroni-corrected comparisons. Most importantly, there was a significant three-way interaction of the factors Hemisphere x Visual Field x Sex. First, RH and LH were compared for the different visual field conditions. Here, both sexes showed no hemispheric N170 differences in the BVF condition and larger RH than LH N170 amplitudes in the LVF condition. In the RVF condition, however, only female participants showed significantly larger left-hemispheric compared with right-hemispheric N170 amplitude, whereas male participants did not show such a modulation in the RVF condition. The effect corresponds to a greater responsivity of left-hemispheric processes underlying the N170 component in female participants only. To follow up on this effect, visual field conditions were then compared within each hemisphere. In female participants, left-hemispheric N170 differed between RVF and LVF; similarly, right-hemispheric N170 differed between LVF and RVF. By contrast, in male participants, RVF and LVF conditions differentially modulated N170 amplitudes only in the LH, but not in the RH. Further results on the behavioral level and latency level are described by Stasch and colleagues.[14]

3.2 Study 2 and 2.1: The encoding of face identity in the duration of N170 adaptation and the role of low-level sensory contributions

N170 adaption effects: As described by Shen and colleagues[14], a repeated measures ANOVAs showed significant main effects of the factors Stimulus, Identity, and ISI. Significant interactions were found for Stimulus x ISI and, most interestingly, for Stimulus x Identity x ISI. The main effect of Stimulus was driven by higher amplitudes of mean S1 compared with mean S2 amplitudes, thus confirming the general RS nature of a paired stimulus paradigm. Post hoc analysis of the main effect Identity showed a significantly lower mean N170 amplitude in identical face trials compared with that in non-identical face trials, thus indicating a modulating effect of face identity on mean N170 amplitude. Post hoc t-tests analyzing the main effect ISI showed a significantly reduced mean N170 amplitude in trials with an ISI of 500 ms compared with the mean N170 amplitude in trials with an ISIs of 2000 ms. The post hoc analysis of the two-way interaction Stimulus x ISI showed no significant differences between N170 amplitudes in response to S1 stimuli, but between N170 amplitudes in response to S2 stimuli after short vs long ISIs, i.e., 500 vs 2000 ms, 800 vs 2000 ms, and 1200 vs 2000 ms, which basically confirms the adaptation of S2 stimuli as a prominent function of the immediately preceding ISI. Importantly, a three-way interaction was observed of Stimulus x Identity x ISI that was followed by post hoc t-tests. N170 amplitudes to S1 were compared with those to S2 stimuli stratified for face identity and ISI. Here, identical face trials showed significant N170 amplitude reductions to S2 compared with the respective S1 stimuli at ISIs of 500 ms, 800 ms, and 1200 ms, thus indicating a late N170 recovery beginning at 2000 ms in identical face trials. In contrast, N170 amplitude in non-identical face trials was significantly reduced only following an ISI of 500 ms, thus indicating an early N170 recovery beginning at 800 ms. These results are strongly indicative of a differential temporal N170 adaptation decay as a function of face identity.

Controlling for low-level contribution to N170 adaption: As described by Shen and colleagues[41], study 2.1 basically replicated the main finding of N170 adaptation as a function of ISI. Significant main effects were found for the factors Stimulus, Identity, and ISI. The factor Size did not significantly contribute to the statistical model. As there was a strong a priori assumption, i.e., a faster decay of N170 adaptation in non-identical compared with identical face trials irrespective of stimulus size, N170 amplitudes to S1 were compared with those to S2 stimuli stratified for face identity, ISI, and stimulus size. Using equally sized stimuli, identical face trials were associated with N170 adaptation following both ISIs of 500 ms and of 1200 ms, although the latter only showed a trend towards statistical significance. In contrast, non-identical face trials were associated with different N170 adaptation effects following an ISI of 500 ms compared with 1200 ms. Very similar results were obtained using stimuli of differing sizes. Pooling trials across stimulus sizes yielded the same pattern for identical faces with short and long ISIs as well as for non-identical faces with short and long ISIs, although, again, some results only showed a statistical trend. Together, only non-identical faces presented with an ISI of 1200 ms failed to show any statistical N170 adaptation independent of equally and non-equally sized face stimuli. By contrast, using identical faces, N170 adaptation following both ISIs of 500 and 1200 ms reached or approached significance. The result of the main experiment, i.e., a faster decay of N170 adaptation in non-identical compared with identical face trials, therefore seems independent of stimulus size and unlikely to be confounded by low-level retinal adaptation effects.

3.3 Study 3: Emotional context in prediction error responses in schizophrenia

vMMN amplitudes: As described by Vogel and colleagues[63], repeated measures ANOVAs of all vMMN components revealed significant main effects of Condition and of Group. Post hoc analysis of the main effect of Condition showed that amplitudes of vMMN components evoked by emotional deviants, sequence emotional and sequence deviants did not differ after correcting for multiple comparisons. Post hoc analysis of the main effect of Group revealed that vMMN amplitudes in controls were significantly more negative compared with vMMN responses in schizophrenia patients. Planned comparisons of group differences within the factor Condition revealed that amplitudes of vMMN components evoked by sequence deviants were significantly more negative in controls compared with schizophrenia patients, which is in accordance with previously reported vMMN deficits in schizophrenia. Most interestingly, ERP responses evoked by emotional deviants and emotional sequence deviants did not differ between groups.

vMMN latencies: The model revealed a significant main effect of Condition, where emotional deviants were associated with a significantly earlier MMN response compared with those evoked by sequence deviants. Combined emotional sequence deviants had an intermediate latency that significantly differed from MMN latency evoked by sequence deviants and emotional deviants.

4 Discussion

4.1 Summary

This dissertation aimed at extending the functional significance of mid-latency components of the visual ERP in face processing by implementing novel paradigmatic approaches. Study 1 examined the hemispheric lateralization of the N170 by using tachistoscopically presented stimuli and thereby found evidence for a differential functional lateralization of face processing as a function of both sex and visual hemifield stimulation. Study 2 aimed at investigating the sensitivity of the N170 for face identity by employing repetitions of identical and non-identical faces with manipulated ISIs. This study clearly demonstrated an encoding of face identity by the N170 as evidenced by the duration of the N170 adaptation and by ruling out confounding effects of potential low-level sensory processes. Within the scope of this dissertation, i.e. to empirically expand the paradigmatic and analytical spectrum of the ERP toolbox, cortical predictive coding processes were examined based on facial affect in a novel emotional sequence oddball paradigm. Study 3 translated previous findings of a facilitated cortical prediction error in response to emotional faces into a clinical sample. It thereby provided evidence for an affective dissociation of the cortical prediction error signature in schizophrenia patients who exhibited large amplitude deficits in neutral trials, but no such difference in trials with emotional face stimuli. Together, these three studies suggest that the ERP components of interest seem to be of broader relevance for lateralization, adaptation and prediction processes, as opposed to a relatively large body of previous research. Specifically, all three studies contribute to and support the hierarchical predictive coding model (figure 1), as discussed later.

4.2 Implementing novel paradigmatic approaches

In all three studies, significant and additive evidence was obtained by modifying established methodological paradigms and specifically tailoring these tasks as innovative contributions to controversially debated research fields. Study 1 employed a tachistoscopic hemifield paradigm which was prior put to work in order to investigate the lateralization of speech processing.[25] To the best knowledge of all authors, the combination of a tachistoscopic hemifield paradigm employing famous and unfamiliar faces and EEG recording in females and males has not been put to work prior to study 1. This new approach enabled not only investigating for interhemispheric cooperation during visual processing by comparing stimuli categories (LVF, BVF and RVF) but also made it possible to investigate sex differences. Study 1 thereby provided evidence for a more pronounced hemispheric lateralization in men than in women during N170 for both stimulus categories (famous vs unfamiliar). Several explanations could account for the demonstrated sex differences. Firstly, women might employ processing strategies that involve more verbal skills than men do[79-81], which might result in more involvement of the LH in women. Secondly, as postulated by Godard and Fiori[29], structural brain differences in the sexes could account for differences in functional processing. In line with that hypothesis, a number of studies reported that the splenium, which is part of the corpus callosum, is thicker in females than in males[82-84] (for a meta-analysis see: Driesen and Raz[85]). Thirdly, hormone levels (such as fetal hormones or circulating level of steroid hormones or the menstrual cycle) might influence functional brain asymmetry[86] and could therefore account for the observed sex differences.

In study 2, the methodological approach was widened by adding a temporal perspective to an established paradigm which evokes adaption responses. The approach was adapted from prior studies within the auditory domain of ERP research.[87,88] This new temporal aspect made it possible to observe the encoding of face identity in the duration of adaption processes of the N170. Prior to study 2, the employment of RS paradigms to face identity encoding on the level of the N170 has led to seemingly incompatible results. Study 2 then demonstrated that the dissociation (some studies reported adaptation of the N170 amplitude in response to repeated presentations of identical faces[42-48] while others did not[49,51,53]) could be resolved by adding a temporal perspective to experimental designs geared towards neuronal adaptation of the N170. Further extension of that paradigm employing varied stimulus sizes even made it possible to control for retinal contributions. As did study 1, study 2 thereby emphasizes the importance of applying innovative methodological approaches in EEG research in order to elucidate and characterize the underlying mechanisms involved in face processing.

Lastly, the sequence oddball paradigm used in study 3 was inspired by the auditory sequence oddball paradigm used by Wacongne and colleagues[89] that was translated into the visual domain and geared towards enhanced face processing by employing affective rather than neutral faces.[90] This study extended a previous normative study[91], which employed an emotional oddball paradigm with happy and fearful faces and found that eMMN responses to both deviants were attenuated in patients with schizophrenia compared to control subjects. However, since emotionally salient conditions were compared with each other, the design did not allow for directly comparing cognitive and emotional prediction error signatures as did study 3. The results therefore provide first evidence that emotional context enhances cortical prediction error responses in schizophrenia similar to control subjects.[67] Without the novel methodological combinations demonstrated in each studies paradigm results presented in this present dissertation could not have been gained.

4.3 Expanding scientific potential through combining novel paradigmatic approaches

To extend this dissertation's primary goal, a combination of the presented approaches could be highly beneficial to further elucidate the functional role of mid-latency components of the visual ERP in face processing. One example of an interesting combination of the presented approaches would be to investigate adaption responses by employing a tachistoscopic hemifield paradigm and differentiating effects for females and males. In that way, a possible interhemispheric cooperation during adaption processes could be observed, as well as possible sex effects. Comparisons with the current literature are precluded since no comparable studies were found. Beyond adaption processes, applying a tachistoscopic hemifield paradigm could also help elucidate prediction error responses in the same manner as described above. In terms of sex differences, Xu and colleagues[92] have indeed found eMMN responses that seem to be specific to sex. They found that in female subjects sad faces elicited larger eMMN responses than happy faces, but that this difference was not present over the left hemisphere. In male participants the eMMN response was not modulated by facial expression, neither in the left nor in the right hemisphere. However, they did not apply a tachistoscopic hemifield paradigm. By employing that paradigm interhemispheric cooperation while processing facial expressions could have been further elucidated. Another highly interesting example of an innovative combination of the presented methodological approaches would be to investigate MMN responses with varying temporal determinants such as ISIs. In that way the temporal decay of vMMN in response to varying temporal variables could be studied in the same way as did study 2. Gaál and colleagues[93] measured vMMN responses as elicited by letters and pseudo-letters in young and older women with varying stimulus onset asynchrony. Results indicated that the longest stimulus onset asynchrony in the older group was 50 ms, indicating longer information persistence in elderly as compared to younger subjects. Results were interpreted as a comprised efficiency of local inhibitory circuits in elderly, leading to longer stimulus persistence, and hence better visual perception in this particular case. Unfortunately, no male subjects participated in that study.

Further research especially for the domain of eMMN should be performed in the described manner.

4.4 Implications for sex and disorder specific psychiatry and psychotherapy

The innovative merging of different methodological approaches is not only relevant in order to study the neurophysiology of face processing. Beyond the described theoretical advantages the prior discussed combinations could have a major impact on our understanding of delivering treatment to individuals. Sex (biological term) and gender (psychosocial term) specific psychiatry and psychotherapy[94] for example could be further scientifically supported by studying sex effects on a neurophysiological level. Taking into account for example that women might employ processing strategies that involve more verbal skills[79-81] could point to activating that processing mechanism also on a therapeutic level. In men on the other hand it could be beneficial to activate other processing mechanism beyond the involvement of verbal skills. However, as Riecher-Rössler[94] put it: “it is high time for a shift in practice and research” and as the editorial of The Lancet Psychiatry[95] once very appropriately summarized, it was not until 1993 that the US National Institutes of Health decreed that all phase 3 clinical trials should include women and minority groups “to ensure that individuals are included in clinical research in a manner that is appropriate to the scientific question under study.” Treatment strategies, including dosages of medication were not extensively tested in women or minority groups before that. But even today, 25 years later, sex and also gender specific aspects are tremendously understudied in psychiatry and psychotherapy. Riecher-Rössler[94] therefore suggests future research on sex-specific aspects of psychopharmacology and hormonal therapies which is what study 1 also points to when considering that hormones could strongly influence functional brain asymmetry.[86]

In this dissertation, implications for treatment cannot only be derived for sex specific aspects but also for disorder specific treatment techniques. Study 3 demonstrated that emotional context restores vMMN in patients with schizophrenia to near normal levels. A very practical implication deriving from that result could be to apply emotional context to therapeutic material in order to facilitate interventions targeting cognitive deficits in schizophrenia. In line with that implication, Oker and colleagues[96] developed a highly naturalistic paradigm in which subjects play a virtual card game while interpreting emotional expressions from a female virtual agent and thereby reading her intentions. This very innovative experimental set up could be put to work in treatment of schizophrenic patients as suggested by the authors and further evidenced by study 3. Also similar set ups employing virtual reality and targeting other cognitive deficits while applying an emotional context in order to facilitate the intervention might be promising (for a review on virtual reality treatment in psychosis refer to Veling and colleagues[97]).

4.5 Implications for the predictive coding network

The present results are also of importance for the predictive coding framework (figure 1). As stated in the introduction, prediction errors can be seen as the discrepancy between predictions made by higher cortical areas and the data that the brain receives from its sensory inputs. Hemispheric lateralization (and its sex differences) and consequently interhemispheric cooperation in response to face stimuli serve as a topographical quantifier of sensory input which is used to form predictions about forthcoming sensory events. Comparisons between sensory-based predictions and upcoming sensory data then lead to reduction (e.g. repetition suppression) or increase of the brain's prediction error response. Study 1 therefore may be seen as a starting point for investigating, e.g., differential hemispheric and sex-specific contributions of the N170 amplitude to the magnitude of subsequent prediction error responses, i.e. potential asymmetries of prediction error responses during face processing. Study 2 also confirms assumptions from the predictive coding framework on the level of repetition suppression (figure 1). In the logic of the hierarchical predictive coding framework, top-down backward connections carry predictions (e.g. the repeated presentation of identical face stimuli), that explain away prediction errors (repetition suppression) and therefore result in adaptation. Here, study 2 showed that adaptive N170 processes behaved as functions of both identity and time, i.e. top-down predictions were stable over 500 ms, but not 2.000 ms. Study 3 contributes to the literature on bottom-up forward connections that convey prediction errors such as the eMMN (figure 1). Study 3 thereby makes a direct contribution to the predictive coding model by providing evidence of compensated prediction error computation in patients with schizophrenia by using stimulus material with emotional content. This result contrasts the extensively replicated deficit of prediction error computation in schizophrenia when emotionally neutral stimuli are used. Thus, to fully translate predictive coding models to clinical populations, both cognitive and affective processing pathways need to be considered.

4.6 Limitations

All three studies show limitations that can be best described under two domains: subjects and stimuli. Considering the domain subjects first: No data was collected on menstrual cycle of female participants, which constitutes a limitation to the present studies since this might influence functional brain asymmetries. In study 3, a potential confound constitutes that undetected sex differences cannot be ruled out due to an imbalanced sample with an overrepresentation of male participants. Although some studies suggest that sex differences seem to be preserved in schizophrenia[98,99], the imbalance of sex distribution in our sample might limit interpretation of this study. Also, age is known to have a decreasing influence on cerebral asymmetries (HAROLD (hemispheric asymmetry reduction in older adults[100])), which poses another limitation to study 1 in which our final sample was different in age between sexes with male participants being significantly older than female participants. However, since the effect is decreasing in nature, the demographic age difference could only have reduced the sex difference observed in study 1 and is therefore not likely to be a critical confound. Turning to the domain of stimuli second: In none of the experiments non-face stimuli were used in the paradigm, which is why it cannot be ruled out that even though our face stimuli are very similar to the ones used in comparable studies[45,101], that we actually measured generic ERPs (e.g. N1) instead of face sensitive components (e.g. N170). In study 3, in order to rule out an effect of the negativity bias in schizophrenia, it would be crucial to investigate the impact of emotion on basic cortical computations, including multiple emotions with different valence (e.g. happy, sad, fearful and neutral).

4.7 Conclusions and future research

In conclusion, the present dissertation expanded the functional significance of ERPs in face processing threefold: Firstly, the N170 served to detect a stronger hemispheric lateralization in men than in women during that stage of face processing, irrespective of the stimulus category. Secondly, it was demonstrated that N170 responses encode face identity mirrored in the duration of the N170 adaptation. Thirdly, evidence was provided that facial affect in face processing restores cortical prediction error responses in schizophrenia. The dissertation provides strong evidence that underlying processes of face recognition can be researched even in more depth by applying novel paradigms. The dissertation also underlined the significance of the predictive coding model for face processing as a suitable framework. The present work emphasises four future research directions. Firstly, structural asymmetries in males and females should be further investigated. Secondly, RS studies should take advantage of the temporal dimension, i.e., adaptation decay over time, to allow for a more precise dissection of neuronal function into feature specific sensitivity versus non-sensitivity. Moreover, the impact of different emotions on the prediction error provides interesting research opportunities for the future. Lastly, the combination of the presented methodological approaches should be considered in future research.

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I Eidesstattliche Versicherung

„Ich, Joanna Vogel, geb. Stasch, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Neurophysiology of face processing: Extending the functional significance of event-related potentials in lateralization, adaptation, and prediction processes" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autorinnen und Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)" des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autorin bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

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Datum Unterschrift

II Anteilserklärung an den erfolgten Publikationen

Joanna Vogel, geb. Stasch hatte folgende Anteile an den folgenden Publikationen:

Publikation 1: Stasch, J., Mohr, B.*, & Neuhaus, A. H.* (2018). Disentangling the interaction of sex differences and hemispheric specialization for face processing–evidence from ERPs. *Biological Psychology,* 136, 144-150.
Beitrag im Einzelnen: Unter fortlaufender Anleitung von Herrn PD Dr. Andres Neuhaus und Prof. Dr. Bettina Mohr: Erstellung des Experiments, Datenerhebung in Zusammenarbeit mit Magdalena Frankiewicz und Lea Rabe, Datenbereinigung, Datenfilterung, statistische Auswertung der behavioralen und elektroenzephalographischen Daten, Erstellung des Manuskriptes und der dazugehörigen Abbildungen, Ersteinreichung und Überarbeitung im Reviewprozess

Publikation 2: Shen, C., Stasch, J., Velenosi, L., Madipakkam, A. R., Edemann-Callesen, H., & Neuhaus, A. H. (2017). Face identity is encoded in the duration of N170 adaptation. *Cortex,* 86, 55-63.
Beitrag im Einzelnen: Ergänzendes Experiment auf Seite 58 unter Punkt 2.5., hiervon die Datenerhebung, -bereinigung und statistische Auswertung, außerdem Mitverfassen des Manuskriptes

Publikation 3: Vogel, B. O., Stasch, J., Walter, H., & Neuhaus, A. H. (2018). Emotional context restores cortical prediction error responses in schizophrenia. *Schizophrenia Research*, 197, 434-440.
Beitrag im Einzelnen: Mithilfe bei der Datenerhebung, Dateninterpretation und Miterstellung des Manuskriptes

* Diese Autorin und dieser Autor teilten die Letztautorinnen und -autorenschaft.

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

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Unterschrift der Doktorandin

III Ausgewählte Publikationen

Publikation 1

Stasch, J., Mohr, B.*, & Neuhaus, A. H.* (2018). Disentangling the interaction of sex differences and hemispheric specialization for face processing–evidence from ERPs. *Biological Psychology,* 136, 144-150.

Impact Factor+: 2.891,

Topjournalkriterium erfüllt im Fachgebiet *Psychology,* Platz 19 von 78

Publikation 2

Shen, C., Stasch, J., Velenosi, L., Madipakkam, A. R., Edemann-Callesen, H., & Neuhaus, A. H. (2017). Face identity is encoded in the duration of N170 adaptation. *Cortex,* 86, 55-63.

Impact Factor+: 4.907,

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Publikation 3

Vogel, B. O., Stasch, J., Walter, H., & Neuhaus, A. H. (2018). Emotional context restores cortical prediction error responses in schizophrenia. *Schizophrenia Research*, 197, 434-440.

Impact Factor+: 3.958,

Topjournalkriterium erfüllt im Fachgebiet *Psychiatry,* Platz 33 von 142

* Diese Autorin und dieser Autor teilten die Letztautorinnen und -autorenschaft.

+Die Angaben beziehen sich auf das Jahr 2017.

Stasch, J., Mohr, B., & Neuhaus, A. H. (2018). Disentangling the interaction of sex differences and hemispheric specialization for face processing–Evidence from ERPs. *Biological psychology*, *136*, 144-150.

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Shen, C., Stasch, J., Velenosi, L., Madipakkam, A. R., Edemann-Callesen, H., & Neuhaus, A. H. (2017). Face identity is encoded in the duration of N170 adaptation. *Cortex*, *86*, 55-63.

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Vogel, B. O., Stasch, J., Walter, H., & Neuhaus, A. H. (2018). Emotional context restores cortical prediction error responses in schizophrenia. *Schizophrenia research*, *197*, 434-440.

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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