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The possible subtypes of the developmental prosopagnosia in the light of the neuropsychological, electrophysiological and imaging estimations

PhD Thesis

Thesis booklet

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Budapest, 2016

Synopse of the presented studies and theses

In the four studies presented in the thesis we investigated the neural background and efficacy of the processes related to the *core region* of the inferior-temporal lobe (IOG-FFA-STS; Haxby, Hoffman, & Gobbini, 2000) operating in the structural encoding phase (Bruce & Young, 1986) of face recognition. We investigated control samples, and samples with congenital prosopagnosia by means of an extended neuro-psychological test battery, electrophysiological measurements and imaging paradigms.

In the acquired form of prosopagnosia (acquired prosopagnosia; AP) face recognition function is normal until certain brain trauma elicits the face recognition deficit. During developmental prosopagnosia (DP) the development of brain circuitry and the related functions which are responsible for face recognition do not follow the neurotypical way from the early postnatal period.

The developmental form of the disorder affects 2-3% of the population, generally owing to *de-novo* mutation (sporadic form). In the rare familiar form, the disorder manifests in several members and generations of the affected family (Kennerknecht et al., 2006).

Investigating the developmental form of the disorder gives rise to have valuable information about the neural circuitry as well as genetic background of face recognition.

However, owing to the rare incidence of DP, the number of investigations is limited, furthermore, the accomplished studies did not exploit the potential of the state-of-the-art electrophysiological and imaging techniques; the genetic background of the neural representation of face recognition is yet to be clarified. Though the incidence of the disorder is relatively high, most of the experimental data, concerning this topic, originates from studies of low sample size ($n<10$). Not suprisingly, the conclusions suffer from limitations.

Because of the heterogenity of the cases described in the literature the therapeutic procedure of prosopagnosia is not determined. Similarly to the functional grouping of object recognition disorders in one part of the AP patients the perception phase of face processing is abnormal (apperceptive type). In the remaining cases further memory and access processes are involved (associative type) (De Renzi, Faglioni, Grossi, & Nichelli, 1991). It is still not clear, whether the classification of object recognition disorders is suitable for the classification of face recognition disorders.

A verifying study about the classification of developmental prosopagnosia along perceptual and associative processes have not been performed yet.

In the first experiment we tested the perceptual phase of visual processing and related electrophysiological correlates in neurotypical sample. According to former studies, complications of general or visual stimulus processing are reflected differentially in the early visual responses (Bankó, Gál, Körtvélyes, Kovács, & Vidnyánszky, 2011; Philiastides, Ratcliff, & Sajda, 2006). Effect of stimulus uncertainty and additional stimulus noise and the related category sensitivity were tested with the aid of an evoked response paradigm. These two kind of manipulations are appropriate „stress test" tools with which category-specific efficacy of stimulus processing can be evaluated. Long-range plan of this experiment was to develop a diagnostic tool suitable for DP functional differential diagnosis. The next two series of experiments are related to each other; face-sensitivity of the *core regions* has been evaluated with the aid of neuropsychological tests, block-design fMRI and evoked response EEG experiments, in two generations of the same family suffering from hereditary DP. Formerely, only the non-hereditary form of DP was studied with low sample size fMRI and/or EEG studies(Avidan & Behrmann, 2009; Avidan, Hasson, Malach, & Behrmann, 2005; DeGutis, Bentin, Robertson, & D'Esposito, 2007; Kress & Daum, 2003; C. Thomas et al., 2009), so the priory aim of our experiment was to investigate the function of the *core regions* of the face recognition system in three members of the family with hereditary DP. As we stated above, the former studies suffer from the limitations of low sample size and thus the functional classification is hard to perform. In the last study we investigated the feasibility of the classification of congenital prosopagnosia into apperceptive and associative subtypes in a large sample of prosopagnosic volunteers (uniquely in the literature) using complex neuropsychological test battery and a face detection ssVEP paradigm. Face detection is one of the first stage of face recognition process which operates extremely effective (Crouzet, Kirchner, & Thorpe, 2010). Face detection abnormality may be proportional with the severity of prosopagnosia. In our study we investigated face detection performance and its electrophysiological correlates in prosopagnosic subjects showing decreased performance in the perceptual test of face recognition, and of those showing control level performance in this test.

Thesis point number one: Added noise and the uncertainty of stimulus age affects behavioural and evoked responses of faces and non-face stimuli differently in neurotypical sample.

In the first experiment we investigated the category-sensitivity of neural processes during the early phase visual processing measuring the evoked responses (P1-N170-P2) in healthy subjects. Based on previous studies (pl. Allison, Puce, Spencer, & McCarthy, 1999; Bentin, Allison, Puce, Perez, & McCarthy, 1996; McCarthy, Puce, Belger, & Allison, 1999) we expect to measure higher N170 response to face stimuli, as compared to non-face stimuli. Recent results, however, contradict the face-selectivity of N170 response (Dering, Martin, Moro, Pegna, & Thierry, 2011; Kloth, Itier, & Schweinberger, 2013; Rossion et al., 2000; Thierry, Martin, Downing, & Pegna, 2007). In these studies images of cars have been also used as control stimuli, along with face stimuli. Formerly, effect of noise on face stimulus processing has been tested (Bankó et al., 2011; Jemel et al., 2003; Schneider, DeLong, & Busey, 2007). However, it was not clarified whether added noise affects the processing of non-face stimulus categories in a similar way as it modulates the processing of faces. Therefore, in our experiments we tested the effect of additional stimulus noise and complications of the stimulus in a common dimension (age) on different visual categories. We found classic face-effect on P1 and P2 amplitudes and on P2 latencies, however, we did not find any differences between N170 amplitudes evoked either by face stimuli or by images of cars. This founding corresponds to the above mentioned literature data. Additional stimulus noise elevated the P1, P2 and N170 amplitudes, furthermore P1 and N170 latencies were also increased. Though the stimulus noise robustly altered the responses to images of cars in the N170 time window, we did not found category specific noise modulation of P2. P1 amplitudes proved to be noise-modulated dependent on brain hemisphere and category-specificity. In the left hemisphere the stimulus noise elevated the response to face stimulus and left the car image responses unaltered. In the right hemisphere we found the opposite pattern.

The paradigm proved to be suitable to test the category specificity of noise processing, furthermore, involving prosopagnosic sample, the paradigm may serve as a suitable tool for investigating the neural background of face recognition disorder. We would like to emphasize that the category selectivity of N170 can not be stated if frontal images of cars are used as control stimulus category. This phenomena is yet to be clarified. Possible explanation may be, that frontal car images and faces are rather similar in configuration (Kloth et al., 2013), and/or cars possess low inter-stimulus perceptual variance similar to those of faces (Thierry et al., 2007).

Thesis point number two: The face-sensitive neural response of the *core* regions of face processing is altered in hereditary prosopagnosia.

The results of MRI studies aiming the description of the neural background of prosopagnosia are inconsistent. In one part of the studies serious structural alterations (e.g. decreased volume of the temporal lobe (Bentin, Deouell, & Soroker, 1999) or the fusiform gyrus (Behrmann, Avidan, Gao, & Black, 2007), damaged occipital face region (Rossion et al., 2003)) do not result in altered face-sensitivity of the unaffected *core regions*. In other studies insufficient face-sensitivity has been described in patients with prosopagnosia without any visible structural malformation (Bentin, Degutis, D'Esposito, & Robertson, 2007; Hadjikhani & de Gelder, 2002). Using neuropsychological tests and magnetic resonance imaging technique we investigated the face-sensitivity of the *core regions* in three family members (father, son and daughter) suffering from hereditary developmental prosopagnosia and, that in matched control subjects. During blood oxygen level dependent response measurements faces, artificial objects and noise images were presented. In the neuropsychological test we found serious disturbance of face perception and face recognition in the three family members. The decreased performance was most severe in the famous faces test (CFFT; B. Duchaine & Nakayama, 2005) and in the face memory test (CFMT; B. C. Duchaine & Nakayama, 2006), furthermore, age decision performance on the PFPB sub-tests (A. L. Thomas, Lawler, Olson, & Aguirre, 2008) was also decreased. Compared to control subjects, subjects with prosopagnosia had decreased blood oxygen dependent activity at the areas of FFA, OFA and lateral occipital complex. Analysing the hemodynamic responses we can conclude, that the neural response is not only decreased, but the decay is more intensive in the *core regions* compared to LO regions in the prosopagnosic subjects. In summary, we can conclude that, the *core regions* of face recognition and the dysfunction of LO are strongly involved in the aetiology of hereditary prosopagnosia.

Thesis point number three: failed face-sensitivity of *core* face processing areas, revealed by fMRI, can confirm in an ERP experiment. The cause of the impaired face-sensitivity can be specified and this is informative regarding the neural properties of the disease.

The electrophysiological correlates of congenital prosopagnosia are not consistent. In several experiments face-sensitivity in prosopagnosic subjects seems to be the same as that of control subjects (Harris, Duchaine, & Nakayama, 2005; Minnebusch, Suchan, Ramon, & Daum, 2007; Towler, Gosling, Duchaine, & Eimer, 2012). However, in other experiments electrophysiological responses generated by face and non-face stimuli were the same in the 120-200 ms wide time window (Bentin et al., 2007; Bentin, Deouell, & Soroker, 1999; Kress & Daum, 2003). Common feature of the examined cases of developmental prosopagnosia, where N/M170 face-sensitivity failed, is the cause of the impaired face-sensitivity. In these subjects the non-face-evoked response was elevated, while the face response remained at normal level. This phenomena indicates the damage of a brain area (and related function) which is involved in the preliminary information filtering just before the information would reach the *core area* "dedicated" to face processing (B. Duchaine, 2011).

In accordance with the previous theory, we measured the face-sensitive N170 parameters in an ERP experiment. With this experiment we wanted to analyse the decreased face-sensitive fMRI performance of the prosopagnosic family members (see above) in detail.

During the measurement we recruited age, gender and IQ matched control subjects. Face and Fourier phase-randomised noise images were used as stimuli. In accordance with previous studies, when face stimulus was presented to healthy subjects, the N170 amplitudes recorded on the occipito-temporal channels were larger than those of registered after noise image presentation. This phenomena was completely lacking in the prosopagnosic members of the family. The cause of the impaired category-sensitivity was the increased amplitude of the noise evoked responses in all family members. Further data analysis clarified that these changes occur due to elevated time-synchrony of single responses and due to the elevated amplitudes of theta oscillations measured in the 130-200ms time window. Our results suggest that the ultimate N170 generator neuron populations, located in the *core regions* of face processing network receive incorrectly selected information during the hierarchical processing. Other possibility is that these neurons can not be activated selectively. Owing to this abnormality face processing utilizing these systems can not operate correctly.

Thesis point number four: Investigating large sample of congenital prosopagnosia and using complex behavioural test battery and a ssVEP face detection paradigm the apperceptive and the associative type of the congenital prosopagnosia can reliably dissociated.

According to the classification of Lissauer (1890) one can distinguish between the two subtypes of object recognition disorders: in the apperceptive form the early visual-perceptual processes are harmed, while in the associative form the access of semantic representations (name, art of usage etc.) is hampered. Hundred years after Lissauer, Benton (1984) and De Renzi et al. (1991) considered a similar classification suitable to distinguish between apperceptive (prosopagnosia) and associative (prosopamnesia) subtypes of face processing disorders. They emphasized also the clinical utility of such grouping. Recently, even more researcher states a clear need for subgrouping of developmental prosopagnosia (Barton, Cherkasova, Press, Intriligator, & Connor, 2003; B. C. Duchaine & Nakayama, 2006b; Fox, Moon, Iaria, & Barton, 2009). However, the number of studies investigating the possible subgrouping of DP is very low. In the fourth series of experiments we tested the possibilities of functional classification of developmental prosopagnosia. In these experiments a large sample of prosopagnosic volunteers and uniquely matched control subjects were involved. In one half of the prosopagnosic group the perceptual performance of face processing showed marked impairment (apperceptive type), while in the other group we measured a performance matching to healthy subjects (associative type). Since face detection is one of the first order face recognition processes which operates extremely effective, we investigated how face detection operates in prosopagnosic subject grouped by perceptual performance. Behavioural test results and EEG, ssVEP test results were analyzed along the apperceptive/associative grouping. Face detection threshold was adjusted with a ssVEP paradigm. During 6Hz noise-image stimulation a 3 HZ face stimulation was introduced with gradually increased visibility. In our analysis we used the performance-modulation effect of the 3Hz oscillation to adjust detection threshold. In the apperceptive prosopagnosic subjects we found decreased performance in the majority of behavioural tests (CFFT performance; (B. Duchaine & Nakayama, 2005). Reaction time (fitting the inner parts of the face), face-inversion effect (CFPT (B. C. Duchaine, Germine, & Nakayama, 2007)), recognition of sadness and disgust during emotion recognition tasks, were also impaired, compared to matched control subjects. In the associative prosopagnosic subjects we measured control level performance all except memory processes (decreased performance in the CFMT test (B. C. Duchaine & Nakayama,

2006)). In the ssVEP study, we found higher face detection threshold values registered from the right hemisphere in apperceptive prosopagnosic subjects. This phenomena indicates that in certain proportion of congenital prosopagnosia the first order processes are responsible for abnormal face recognition. However, in subjects, showing normal face detection the latter associative processes are impaired. Our results may be indicative for the functional grouping of congenital prosopagnosia. These results may also serve as a base for further group-specific training programs.

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