Latent Inhibition in schizophrenic patients and healthy controls: an event-related fMRI study

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Introduction

- Latent inhibition (LI), retarded learning after preexposure to the to-be-conditioned stimulus, is an important model for understanding attentional deficits in schizophrenia (e. g. positive symtoms; cf. Lubow, in press). Disruption of LI which has been observed in actively psychotic but not in chronic, medicated patients is thought to result from an inability to ignore irrelevant stimuli.
- The study investigates the brain regions relevant to LI, as indexed by reaction times and autonomic measures (electrodermal responses), in chronic, medicated schizophrenic patients and in healthy controls, using an event-related fMRI-design.
- Animal models of LI (cf. Weiner, 2000) postulate the relevance of subcortical structures, i. e. hippocampus, amygdala, and, particularly, the nucleus accumbens.

Methods

- **Sample 1**: N = 26 medicated schizophrenic patients (males: paranoid/residual type n = 25/1)
  - Age (years): M = 33.5 (range 20 – 54)
  - Duration of illness (years): M = 9.5 ± 6.6
  - Number of hospitalizations: M = 6.5 (range 1 – 35)
  - Psychopathology
    Positive symptoms (SAPS; cf. Andreasen, 1993):
    M = 8.1 ± 14.2 (range 0 – 58 of 155)
    Negative symptoms (SANS; Andreasen, 1989):
    M = 22.2 ± 16 (3 – 68 of 95)
  - Neuroleptic medication: M = 2,4 ± 1.7 DDD-Units[1]
    typical: f = 1 ; atypical: f = 21; combination: f = 4
- **Sample 2:** N = 26 male control subjects, matched by age and smoking behaviour

[1] A Defined Daily Dose of 1 ,is the assumed average maintenance dose per day for a drug used for its main indication in adults"(cf. WHO: http://www.whocc.no/atcddd).

- **Design**

During preexposure two frames of different colour were presented 15 times each. Images of landscapes, animals, or human beings were located in the middle of the frames. Subjects were instructed to look carefully at them and to count the human beings (masking task[2]). In the acquisition phase that followed preexposure without interruption, one of the two preexposed, now unmasked frames and one of two novel frames served as to-be-conditioned stimuli (CSp+, CSn+), whereas the other two were the not-to-be-conditoned stimuli (CSp-, CSn-). The un-conditioned stimulus (US) consisted of a reaction time task (8 seconds delay con-ditioning). All of the stimuli were presented 10 times each for a duration of 8 s. Figure 1 demonstrates this design.

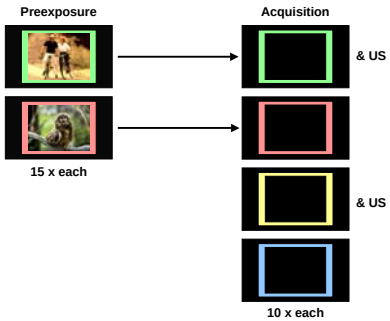

Fig. 1. **LI within-subject design**

[2] The masking task enables an automatic processing of the preexposed stimuli, which is necessary for LI to arise (cf. Lubow und Gewirtz,1995)

- **Measures**
  - Reaction times (RT) to the US
  - Electrodermal activity (EDR) during acquisition phase
    first-interval response (FIR): 1 – 4 s after CS onset
    second-interval response (SIR): 4 – 9 s after CS onset
    third-interval response (TIR): 9 – 13 s after CS onset
  - functional imaging (fMRI) data during acquisition

- **fMRI: Data acquisiton and analysis**
  - Siemens Symphony 1.5 T Scanner
  - T2*-weighted single shot gradient echo EPI sequence
  - 30 slices with 4-mm thickness, 1-mm gap, in descending order
  - 64 x 64 matrix, FOV = 192 mm → 3 x 3 x 4 mm voxel
  - TA = 100 ms, TE = 50 ms, flip angle = 90°
  - TR = 3 s, 443 volumes, duration 22:21 min
  - Data analysis with SPM2: Wellcome Department of Imaging Neuroscience, London
  - Preprocessing: realignment; slice time correction; normalising; smoothing (9-mm Gaussian kernel)
  - Modelling: event-related design with a synthetic hemodynamic response function, for the 4 CS conditions and for the US condition, separately for the first (trials 1 – 5) and the second part (trials 6 – 10) of the acquisition phase[3]
  - 6 movement parameters (3 translations, 3 rotations) as covariates
  - Random-effects second level analysis: region of interest analyses

[3] This is because the LI effect is a window phenomenon.

Literatur

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Results

- RT: Both groups exhibited RT-LI, however it was restricted to the first half of the acquisition phase (see Figure 2a). Here, subjects responded more slowly to preexposed (CSp) than to non-preexposed (CSn) stimuli. The effect sizes of the RT-LI effect were similar.
- EDR: Two control subjects and ten patients had to be excluded from the EDR analyses because they were non-responders (lack of at least 50 % of the unconditioned responses and/or no orienting and no conditioned responses). Among the other subjects, the reaction time task elicited reliable unconditioned responses, both in the control as well as in the patient group ($F(1, 23) = 64.1$, $P \leq 0{,}001$; $F(1, 15) = 19.01$, $P \leq 0{,}001$, respectively). Only the control subjects showed a response differentiation between CS+ and CS- in FIRs and SIRs, and there was an LI effect for the SIRs which parallels the RT-LI effect. Conditioning effects were higher in the non-preexposed (CSn+, CSn-) compared to the preexposed (CSp+, CSp-) condition in the first half of the acquisition, whereas in the second part the conditioning effects were higher in the preexposed condition (see Figure 2b).
- fMRI data: If the response differentiation in the preexposed condition (CSp+ minus CSp-) is contrasted to the response differentiation in the non-preexposed condition (CSn+ minus CSn-), patients and controls show an activation of the nucleus accumbens and of the amygdala. Contrary to control subjects, patients also show an activation of the hippocampus.

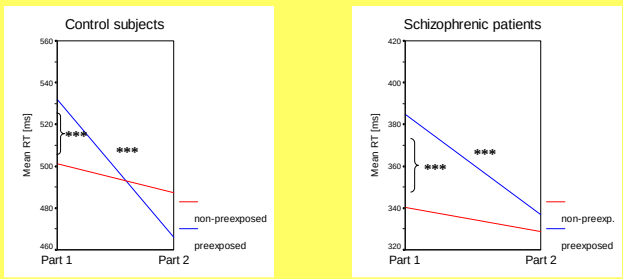

Fig. 2a. Reaction times (RTs) in CSp and CSn condition of the 1st and the 2nd part of the acquisition
Interaction: controls $F(1, 25) = 10.87$, $P \leq 0{,}01$; patients $F(1, 25) = 11.69$ $P \leq 0.01$
Effect size ot the RT-LI effect (controls, patients): Eta-square = 0.30, Eta-sqare = 0.32

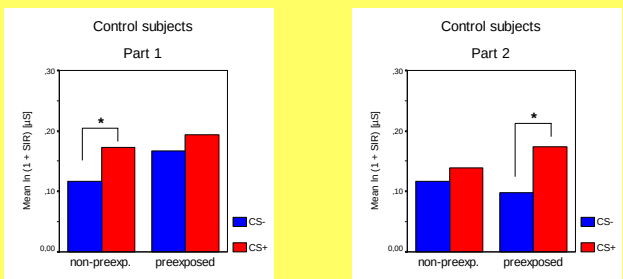

Fig. 2b. Control subjects: electrodermal SIRs in preexposed (CSp+, CSp-) and non-preexposed (CSn+, CSn-) condition of the 1st and the 2nd part of the acquisition; Interaction: $F(1, 24) = 4.08$, $P = 0.055$)

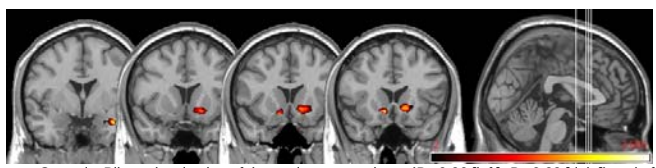

Fig. 3a. Controls: Bilateral activation of the nucleus accumbens ($P = 0.06$ [left], $P = 0.09$ [right]) and of the right amygdala ($P \leq 0{,}05$) during the 1st part of the acquisition: CSp+ > CSp- > CSn+ > CSn- (P-values corrected for ROI)

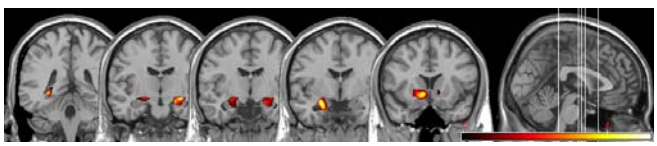

Fig. 3b. Patients: activation of the left nucleus accumbens ($P \leq 0{,}01$), of the amygdala ($P \leq 0{,}01$ [left], $P \leq 0{,}05$ [right]), and of the hippocampus ($P \leq 0{,}01$ [left], $P \leq 0{,}05$ [right]) during the 1st part of the acquisition: CSp+ > CSp- > CSn+ > CSn- (P-values corrected for ROI)

Discussion

- The fact that RT-LI is evident in both the control and the patient group can be interpreted as a normalization of the LI effect in chronic, medicated schizophrenic patients, which is in line with most of the LI literature.
- In the control group, the LI effect for the SIRs, which parallels the one for the RTs, indicates that both measures reflect the same underlying LI process. There was no conditioning effect in the patient group as a whole. However, if negative symptomatology is taken into account, there was a significant interaction 'Preexposition x Conditioning x Group' ($F(1, 15) = 5.16$, $P \leq 0.05$) indicating that LI is evident only in the group with a high negative symptom level.
- According to Gray's (1991) model, the activation of the nucleus accumbens is interpreted as the inhibiting effect of this structure on processing of preexposed stimuli. The activation of the hippocampus then would reflect the detection of a mismatch between the contingency of the preexposure (stimulus-no consequcene) and of the acquisition phase (stimulus-consequence). Finally, amygdala activation presumably reflects that it is more difficult to predict the US after a preexposed and therefore inhibited stimulus than after a novel stimulus and that a non-predictable stimulus is emotionally more relevant than a predictable one.