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Running head: LOW-LEVEL TEMPORAL CODING IMPAIRMENTS IN PSYCHOSIS

Low-level temporal coding impairments in psychosis: Preliminary findings and recommendations for further studies.

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Abstract

We investigated whether difficulties with temporal event-coding, previously reported in patients with schizophrenia, are already present during first-episode psychosis (FEP). In this experiment, the subjective judgements of the simultaneity of visually presented stimuli were compared between 11 healthy controls, 9 chronic schizophrenia (CSZ) and a sample of 11 FEP patients. Participants were asked to indicate whether two vertical bars appeared at the same time or at different times on a computer monitor. CSZ patients' thresholds were elevated while the FEP sample also showed higher thresholds relative to controls. Although preliminary, these findings indicate a generalised disturbance in event-structure coding at early stages of psychosis and question the specificity of its disturbance. Considering the proposed relationship between event-structure coding and the experience of time in general, our study recommends future studies refocus on psychosis in general rather than on schizophrenia as a particular case of abnormal temporal processing. In addition, we suggest that the relevant psychopathology will be best determined by means of a comprehensive analysis of low-level temporal coding performance in different forms of psychosis.

Keywords: First-Episode Psychosis, Schizophrenia, Event-Structure Coding, Simultaneity Threshold (5 014 words)

Low-Level Temporal Coding Impairments in Psychosis: Preliminary Findings and Recommendations for Further Studies

Patients with schizophrenia present abnormal time perception, overestimating comparisons between test and standard intervals of less than 1 second as well as overestimating a range of intervals in temporal bisection tasks (Elvevåg, McCormack, Gilbert, Brown, Weinberger, & Goldberg, 2003). Impaired interval estimation has been attributed to the impaired function of an internal clock mechanism (Rammsayer, 1990) although this perspective is not universally accepted. Instead, it has been suggested that because test intervals require comparison with standards in long-term memory (Elvevåg et al., 2003), patients with schizophrenia are primarily impaired at the stage of access, determining or applying benchmarks held in memory. Consistent with this are studies examining pulse-pulse interval matching. These show that patients with schizophrenia both over- and underestimate a second pulse-pulse interval (Davalos, Kisley, & Ross, 2002; 2003), which may be argued to be attributable to impairments arising during comparison rather than during time perception. These data appear consistent with the common held idea of schizophrenia as a disorder presenting impairment in memory and related cognitive processes rather than a disorder specific to time processing.

This has raised the question of whether or not a memory-based account fully describes abnormal time estimation in schizophrenia. Of relevance to this question are time estimation errors which reach their maximum over ranges of less than 50 ms (Davalos et al., 2002, 2003). This very short interval suggests that in addition to difficulties in time estimation, patients with schizophrenia also experience problems related to the coding of event-structure at very short durations. Measures of event-structure coding using simple paired events have been reported by Pöppel (1985), who found events were judged to be “simultaneous” up to

onset intervals of between 30 to 40 milliseconds (ms) while the required intervals for detection of an “asynchrony” were of a similar magnitude. Pöppel argues that the experience of time is hierarchical with levels of the hierarchy causally related. At a fundamental level and in order to be able to structure which events come first, one needs to experience simultaneity as compared to asynchrony. If this capability is disturbed the experience not only of simultaneity but the experience of event-structure will become distorted. Given that experience of time develops from temporal coding at lower levels of processing, impairment in judgements of simultaneity should correlate with abnormality at superordinate levels in the hierarchy, which mediate the experience or perception of time. While linkage between these levels is not demonstrated in schizophrenia, studies of low-level event-structure coding indicate that patients will experience two visual stimuli to be simultaneous over intervals that are significantly increased relative to healthy comparisons (Foucher, Lacambre, Pham, Giersch, & Elliott, 2007; Giersch, Lalanne, Corves, Seubert, Shi, Foucher & Elliott, 2009). For example, using the paradigm developed by Elliott, Shi, and Sürer (2007), which does not involve serial test-comparison presentation, and so aims to minimise the role of working memory, Giersch et al. reported substantially increased thresholds of on average 111 ms in patients. This value compares with thresholds in healthy controls of 59 ms and comparable thresholds in healthy subjects in other studies (60 ms: Elliott et al., 2007 and 63 ms: Elliott & Shanagher, in press). The elevated thresholds in patients were uncorrelated with medication dosage or symptom severity and suggest that during the experience of events in time patients experience an extended integration of past with present events that may have a negative impact on the content structure of conscious experience (Husserl, 1928).

Evidence for abnormalities in the coding of event-structure in schizophrenia appear to be independent of memory impairments and support the idea that schizophrenia is additionally characterised by impaired temporal processing. However, the further question remains to what extent elevated simultaneity thresholds are a specific feature of performance

in individuals with schizophrenia. Other research suggests they are not a universal feature of abnormal cognitive performance: for example, assessments of specific-language-impaired and dyslexic children, both samples expected to present abnormal event-structure coding due to the temporal nature of language processing and reading, show no direct evidence for abnormal temporal coding (Elliott & Shanagher, 2010; Martyn, Antonijević & Elliott, 2009). However, schizophrenia is a severely debilitating disorder and a more suitable model with which to make comparisons might be a sample of patient referrals having recently experienced their first episode of psychosis (FEP). Psychosis is an umbrella term used to describe mental illness characterised by a loss of contact with reality (Sims, 2003) due to misinterpretation of perceptions with the most common and “prototypical psychotic disorder” being schizophrenia (Ninan, Mance & Lewine, 1998, p.153). Symptoms are varied and can include delusions (abnormalities in the content of thoughts), hallucinations (perceptual experiences in the absence of external stimuli), disorganised thinking (thinking incoherently) and alterations in emotions and behaviour (Andreasen, 1987). While some FEP patients might later be diagnosed with schizophrenia, the diversity of clinical presentations in patients with various forms of psychosis suggests separate underlying psychopathologies either in terms of the neuroanatomy (e.g., Lohr & Caligiuri, 1997) or neurophysiology. Various theories of schizophrenia exist proposing dopaminergic (Healy, 2002; Jones & Pilowsky, 2000; Kapur & Mizrahi, 2005; Soyka, Zetsche, Dresel & Tatsch, 2000), serotonergic (e.g., Harrison, 1999), GABAergic (e.g., Wassef, Baker, & Kochan, 2003) or glutamate (e.g., Hashimoto, Okamura, Shimizu, & Iyo, 2004) dysregulation as underlying cause of the disorder.

In the present study, we measured the delays between bar onsets required to detect an asynchrony in patients having experienced their first psychotic episode (First Episode Psychosis; FEP), and sought to compare these against delays in healthy controls (HC) and patients with chronic schizophrenia (CSZ). Consistent with previous research, we expected patients with schizophrenia to require significantly longer delays than healthy controls with

the result that their simultaneity thresholds would be higher. However, our main research question concerned the delays required by the FEP patients. If our analysis revealed increased thresholds in patients diagnosed with schizophrenia and not in the other FEP patients, the abnormal coding of event-structure might be attributable to psychopathological factors specific to schizophrenia. If however, the FEP patients showed an average increase in thresholds relative to controls, the present data would argue abnormal event-structure coding to be a performance characteristic of psychosis in general and not particular to schizophrenia.

Participants

Eleven FEP, 11 CSZ patients and 11 HC participated, however, for two CSZ patients thresholds could not be established leaving the data of 11 FEP ($M_{age} = 27.71$, $SD = 8.79$; 6 males), 9 CSZ patients ($M_{age} = 33.32$, $SD = 8.41$; 6 males) and 11 HC ($M_{age} = 28.75$, $SD = 8.87$; 9 males) subject to analysis. The FEP group comprised various diagnoses, illustrated in Table 1. At the time of testing, these individuals had been administered antipsychotic medication for an average (mean) of 22.09 days ($SD = 17.97$) and one patient was medication-free.

-----Table 1 here-----

FEP and CSZ patients were recruited from the in-and outpatient units in the University College Hospital Galway (UCHG), and regional hospitals or outpatient units in Loughrea, Ballinasloe, and Ennis, Republic of Ireland. All patients were diagnosed by psychiatrists from UCHG using the Structured Clinical Interview for DSM-IV Disorders, Fourth Edition (SCID-P, First, Spitzer, Gibbon & Williams, 1995, DSM-IV, American Psychiatric Association, 1994). In order to provide information about symptom severity, PANSS scores (Positive and Negative Syndrome Scale, Kay, Fiszbein & Opler, 1987) were also collected for each patient, coded from 0 (absence of symptoms) to 6 (extreme). For the control group, non-psychiatric comparison participants of comparable age and premorbid intelligence with no DSM-IV diagnoses of past or current mood or psychiatric disorders, as diagnosed by the

SCID-Non-Patient Version (First, Spitzer, Gibbon, & Williams, 1996), were recruited through flyer advertisements, the local newspapers, and from staff and students of the National University of Ireland Galway (NUIG) and UCHG. Controls did not differ on key demographic variables from patients.

Exclusion criteria for both patients and controls were neurological disorders (including epilepsy), learning disability, co-morbid substance or alcohol misuse, co-morbid axis 1 disorders, a history of head injury resulting in loss of consciousness for over 5 minutes, a history of oral steroid use in the previous three months, loss of weight in excess of 12% of the original body weight in the previous year, and history of viral infection in the previous month. Furthermore, controls were excluded if they had a personal, or a known family history of a psychiatric illness among their first and second degree relatives of psychotic illness or non-organic psychotic disorder. FEP patients were defined as experiencing their first episode of a psychotic illness and having received less than 6 weeks of antipsychotic medication at the time of testing. The CSZ group was recruited from a clozapine clinic and thus represent a relatively homogenous group of severe, chronic schizophrenia patients, who had failed to respond to initial antipsychotic treatments. This sample represents about 30% of chronic schizophrenia patients and thus a sizeable subset of the illness. All chronic schizophrenia patients were receiving atypical antipsychotic medication (predominantly clozapine).

The project was approved by both UCHG and NUIG ethics committees and informed written consent was obtained before the study from all participants. The study was carried out in accordance with the recommendations of the Declaration of Helsinki for human rights. All subjects had normal or corrected-to-normal vision.

Apparatus and Stimuli

Stimuli were presented on a Pentium 4 PC running Windows XP equipped with a Cambridge Research Systems (Rochester, Kent, UK) visual stimulus generator (ViSaGe).

Stimulus control and presentation were programmed in the C programming language using the VSG software library. The visual stimuli were presented using a Mitsubishi Diamond Pro 2070SB monitor with the refresh rate set to 120 Hz.

The target stimuli consisted of two vertical grey bars separated by 13° of visual angle at a viewing distance of 100 cm at which each bar subtended $3^\circ \times 10^\circ$ of visual angle. Target bars increased luminance twice: The first change (from a background of 0.06 cd/m^2 – gradually and nonlinearly - to a peak luminance of 14.4 cd/m^2) occurred within a premask comprising the onset, presentation for 75 ms, and then offset in series of 6 flanker bars. The premask bars rendered the first change in target luminance below detection thresholds. The second change in luminance (gradually and nonlinearly from 14.4 cd/m^2 to 29.8 cd/m^2) occurred in the absence of flankers and it was to this change that observers made their judgement of the simultaneity or asynchrony change across the target bars. Stimulus presentation occurred in an environment of low intensity, ambient light (0.1 cd/m^2) to reduce the impact of onscreen persistence.

The premask took the form of 6 flanker bars of identical dimensions to the target bars but the flankers were oriented pseudo-randomly 45° to the left or right of the vertical meridian. The masking bars onset in pseudo-random order and temporally interleaved with the first change in target-bar luminance. The first change in target bar luminance occurred in two conditions: synchronously (SB_S) or asynchronously (SB_A). In SB_S , the two bars started to change luminance simultaneously, while in SB_A the two bars changed luminance at SOAs determined individually by the adaptive staircase procedures described below.

Procedure

Staircase Procedures

Two staircase procedures determined lower and upper simultaneity thresholds between which bar-bar SOAs were set in the main experiment (i.e., the SB_A condition). In the lower threshold procedure, participants judged the simultaneity or asynchrony of a simple

luminance change between two target bars while in the upper threshold procedure, changes in target luminance were embedded in a sequence of flankers while participants were again required to judge their simultaneity or asynchrony. Staircases used the stochastic approximation procedure developed by Treutwein (1995), in which the 2 bars were initially presented with an SOA above threshold and then gradually reduced on a trial-by-trial basis until the subject responded 'synchronous'. An initial threshold of 80 ms initiated this procedure. Both lower and upper thresholds were estimated separately and at least twice in order to ensure more reliable stable parameterisation of SB_A in the main experiment. In both staircase procedures, stimulus presentations were preceded by the 500 ms presentation of a fixation frame (four corner junctions), comprising a $13^\circ \times 13^\circ$ square region, within which the stimuli were presented.

Main experiment

The method of constant stimuli was employed to determine visual simultaneity thresholds. This method uses different levels of a certain property of the stimulus by presenting these in random order from one trial to the next, thereby reducing predictability and habituation. By establishing a data point for each level of the stimulus, it is possible to derive a psychometric function. For the purpose of this research, the stimulus property of interest was the delay between two visual target bars (Stimulus Onset Asynchronies, SOA) ranging from 0-330 ms. A preliminary experiment showed that the range 0-100 ms led to 15 subjects from FEP and CSZ groups being unable to perform the experiment. The simultaneity threshold was taken as the 50 % mark of simultaneous responses for each level of SOA (12 levels) on the psychometric function.

Target bars were presented within the pseudo-randomised sequence of premask flankers as well as following premask presentation. On this second occasion the target bars changed luminance 150 ms after the final flanker had switched off, and fully visible to

participants. Participants had then to report whether this change in luminance occurred simultaneously or whether the target bars had changed luminance with an asynchrony.

The SOAs between target bars were either set at 0 ms (the SB_S condition) or within the range of SOAs circumscribed by the lower and upper thresholds in the SB_A condition (as described previously). The main experiment included 12 target SOAs, each presented 40 times with presentation order randomised on a session by session basis. In addition, an equal number of trials were presented in which the first bar appeared to the left as to the right. The targets were presented at maximum luminance for 2 seconds, during which observers reported whether they perceived luminance-change synchrony or asynchrony of the targets. There was an interval of 12 seconds between trials. This experiment was conducted in one session of 10, 48-trial blocks. Participants initiated each block by manual key press and depressed letter keys 'F' for synchronous and 'J' for asynchronous judgments.

Results

Group Differences in Key Demographic Variables

For those participants for whom thresholds were established (11 HC, 11 FEP and 9 CSZ), the participant groups did not differ significantly with regard to gender ($\chi^2(2, N = 31) = 1.88, p = .391$) or IQ differences between groups ($\chi^2(30, N = 28) = 27.12, p = .617$) as measured by the NART (National Adult Reading Test, Nelson, 1991) using a statistical significance level of .05. There were no significant age differences ($F(2, 28) = 1.514, p = .238$).

Differences in clinical variables between the two patient groups

Non-parametric Mann-Whitney U-tests were run for each clinical variable to investigate potential differences in clinical variables. Bonferroni corrections were made adjusting the significance value to $p < .01 (p / 5)$. No significant differences were found between FEP and CSZ patients with regard to Age of Onset ($U = 47, FEP: mdn = 23, CSZ: mdn = 23, p = .867$) or the PANSS negative ($U = 36, FEP: mdn = 6, CSZ: mdn = 6, p = .722$), positive ($U = 25.5,$

FEP: $mdn = 8$, CSZ: $mdn = 5$, $p = .069$) or general symptom subscales ($U = 23$, FEP: $mdn = 14$, CSZ: $mdn = 5$, $p = .022$).

The FEP group on average were found to be on significantly less medication ($mdn = 200$) than the CSZ group ($mdn = 700$) as measured by CPZ equivalents ($U = 8$, $p = .029$). The means for all clinical variables for the two patient groups are displayed in Table 2.

-----Table 2 here-----

Threshold Calculations

Psychometric functions (PFs) were calculated individually using a least squares fitting procedure. Preliminary inspection of the data revealed a high guess rate, which recommended correction. On this basis, the individual data were submitted to the following probability-based correction after Elliott et al. (2007):

$$P_{adj}(x) = \frac{P(x)}{P(0)} \quad (1)$$

where $P(0)$ is percentage of ‘synchronous response’ for ‘subthreshold simultaneity (i.e., a subthreshold SOA = 0). This was done to eliminate the problem of a bias towards asynchronous responses. Individual thresholds were calculated as the SOAs corresponding to a rate of 50 % simultaneity responses for synchronous and asynchronous premask separately. The overall threshold was defined as the mean of thresholds of synchronous and asynchronous premask. Data were analysed using SPSS version 18 and Statistica Version 9. An alpha level of .05 was used for all statistical tests.

Staircase Thresholds

Staircase thresholds were examined using analysis of variance (ANOVA) with the factors participant group (HC, FEP and CSZ) and premask (no flankers and flankers). There were main effects for group ($F(2, 56) = 6.02$, $p = .004$), showing significantly different thresholds in HC, FEP and CSZ groups, and premask ($F(1, 56) = 43.18$, $p < .001$), indicating significantly different thresholds for trials with and without flankers. The interaction between

group and premask was found to be non-significant ($F(2,56) = .865, p = .427$). Gabriel's post-hoc test found that HC differed significantly from both FEP ($p = .019$) and CSZ ($p = .009$) groups but staircase thresholds (see Table 3) did not differ significantly between the two patient groups ($p = .965$).

-----Table 3 -----

Group Differences in Simultaneity Thresholds

A one-way ANOVA with factors group and premask revealed significant differences in simultaneity thresholds between FEP, CSZ patients and HC groups ($F(2, 14.144) = 13.76, p < .001$). Planned contrasts revealed that patients overall had significantly higher thresholds than controls ($t(23.67) = 4.99, p < .001$, FEP: 85 ms, CSZ: 94 ms, HC 51 ms) but the FEP and CSZ patients did not differ significantly ($t(17.53) = .677, p = .436$). The premask influenced thresholds ($F(1, 28) = 5.80, p = .023$) with thresholds higher for SB_s (HC: 50 ms, FEP: 91 ms, CSZ: 102 ms) relative to the SB_A condition (HC: 52 ms, FEP: 79 ms, CSZ: 87 ms), but this pattern was the same for all groups (the interaction was non-significant).

-----Figure 1 here-----

PFs were overall steeper (see Figure 1) and differed significantly between groups for both SB_s and SB_A conditions (all $t > 2.0, p < .05$), except for SB_s between FEP and CSZ groups ($t = 1.00, p > .05$).

Discussion

This study confirmed previous reports of elevated simultaneity thresholds in patients with schizophrenia but extends upon those studies to show FEP patients with various diagnoses also had significantly elevated thresholds relative to controls. In fact, the major finding in this study is that irrespective of diagnosis, patients having recently experienced a psychotic episode for the first time will require longer SOAs than controls and similar SOAs to patients with chronic schizophrenia to detect an asynchrony. This means that previous studies of event-structure coding and perhaps also studies of time perception in schizophrenia

may need to broaden their explanation beyond schizophrenia to include psychosis in general as subject to disordered time phenomenology. Thresholds were elevated and were non-significantly different between FEP and CZ patients for simple paired events, masked paired events and in the main experiment, in which paired events followed premask sequences.

This study offers preliminary evidence that timing deficits in psychopathology may be better understood as a core deficit in psychosis rather than particular to schizophrenia. However, a number of issues require resolution before our preliminary data can be accepted as veridical: it is possible that individual differences may have been of greater impact in this study than in a study using larger sample sizes and while differences between FEP and chronic schizophrenia patients may vary slightly, it seems unlikely that the elevated thresholds found in FEP patients would reduce on the average to compare with those of healthy comparisons. Due to the nature of the illness, the two patient groups differed on some clinical measures such as general symptoms, as measured by the PANSS, and medication and this raises several considerations:

Firstly, it may seem surprising that the FEP patients on average were more symptomatic than the chronic group but this is due to the effectiveness of antipsychotic medication in the chronic group, more specifically clozapine, one of the few neuroleptics that improve treatment-resistant schizophrenia. However, if it was just the symptoms per se that lead to elevated thresholds then it would be expected that the FEP patients show even higher thresholds than the chronic patients with schizophrenia, which was not the case. This poses the question whether the differences in simultaneity thresholds observed may be due to underlying pathologies in the brain and presentation with psychotic symptoms may be secondary. It could also be the case that particular anatomical changes or cognitive impairments are a better indicator of prognosis than symptoms per se, as symptoms frequently change and may only be representative of the mental state of individuals at the time of assessment.

Secondly, diagnoses in FEP are preliminary and subject to change. Consequently, to be sure that the data presented here are not representative of a sample of FEP patients that will in future be reclassified as having schizophrenia, more extensive study of event-structure coding in various types of psychosis a few years after first presentation is required. Finally, not all patients have the same treatment profiles and depression may also have an effect on patients' task performance. Both are factors that require more systematic examination.

The present study was, to our knowledge, the first study to examine event-structure coding in psychosis and to compare this to chronic schizophrenia patients. We confirmed previous reports of higher thresholds in patients with schizophrenia and, despite differences in medication to previous studies we may be able to extend these findings. In addition and most importantly, these preliminary data show evidence for a generalised deficit in event-structure coding that applies to a variety of psychotic disorders and is not confined to schizophrenia alone. One recommendation leading on from this discovery is that investigations of time-related disorders may need to focus away from schizophrenia alone and refocus on psychosis in general instead as being susceptible to disordered temporal processing. Larger sample sizes are certainly required not only to examine for differences in temporal coding but also to determine the pathophysiology underlying abnormal event-structure coding.

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Comment [M1]: Need updating

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Table 1

Distribution of FEP patients according to DSM-IV diagnostic criteria

Diagnosis	N
Schizophrenia	1
Schizophreniform Disorder	4
Delusional Disorder	2
Bipolar Disorder with severe psychotic features	1
Psychosis Not-Otherwise-Specified	1
Major Depressive Disorder with psychotic features	1
Brief Psychotic Disorder	1

Table 2

Clinical Variables of the two patient groups

	Chronic Schizophrenia Group (n = 9)		First-Episode Psychosis Group (n = 11)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
DUP (FEP)/ Illness Duration (CP) in months	138.56	64.00	9.39	12.59
PANSS positive symptom scale	5.00	4.15	8.36	2.16
PANSS negative symptom scale	5.67	4.72	7.27	5.06
PANSS general symptom scale	7.89	9.16	13.45	4.34
Medication (CPZ equivalents)	809.17	668.52	293.45	310.08
** Age of Onset	26.37	8.78	26.91	10.96

** $p < .01$ (using Bonferroni corrections)

Table 3

Lower and upper simultaneity threshold means (with standard deviations) for each group as determined by the staircase procedures.

	Lower simultaneity threshold	Upper simultaneity threshold
HC	15 ms (5 ms)	100 ms (89 ms)
FEP	56 ms (68 ms)	176 ms (76 ms)
CSZ	54 ms (47 ms)	197 ms (90 ms)

Figure Captions

Figure 1: Psychometric functions for Experiment 2 (0-330ms) as a function of premask type (SB_S filled, SB_A unfilled) for each group depicting from left to right CSZ, FEP patients and HC.

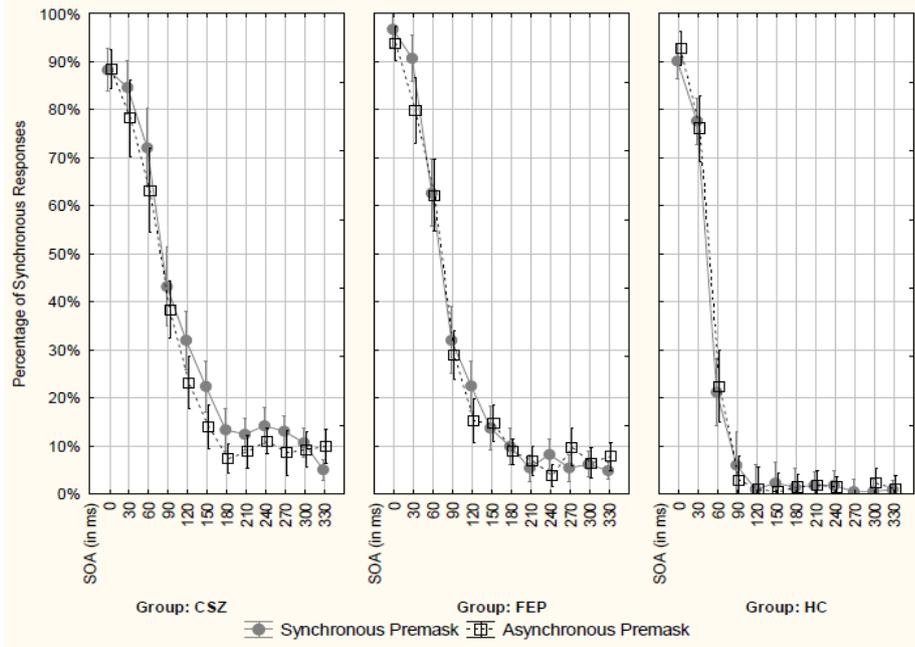


Figure 1: Psychometric functions for the main experiment as a function of premask type (SB_S filled, SB_A unfilled) for each group depicting from left to right CSZ, FEP patients and HC.