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Impaired sensorimotor gating in schizophrenia with deficit and with nondeficit syndrome

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Summary

Questions under study: Prepulse inhibition (PPI) is the normal suppression of the startle reflex when the intense startling stimulus is preceded by a barely detectable prepulse. PPI has been proposed to reflect a measure of sensorimotor gating or filtering. Deficits in PPI has been found in schizophrenia in various prepulse conditions. The aim of this study was to investigate whether deficits in particular prepulse conditions relate to psychopathological syndromes.

Methods: Schizophrenia was subgrouped into patients with deficit and with nondeficit syndrome using the schedule of Kirkpatrick. Schizophrenia with deficit syndrome (N = 46), schizophrenia with nondeficit syndrome (N = 21), and controls (N = 44) were compared in an acoustic startle paradigm assessing PPI (30, 60, 120, 240 and 2000 ms interstimulus intervals). A mixed ANOVA was used to analyse the PPI-data.

Results: Schizophrenia with deficit syndrome showed a PPI-deficit in the 60 ms prepulse condition and a reduced facilitation in the 2000 ms prepulse condition, whereas PPI in patients with nondeficit syndrome was impaired in the 240 ms prepulse condition.

Conclusions: The different patterns of PPI in deficit and nondeficit patients appear to relate to the heterogeneity of schizophrenia. Thus, this study may explain the various findings in previous PPI studies in the field of schizophrenia.

Key words: schizophrenia; deficit syndrome; nondeficit syndrome; information processing; prepulse inhibition

Introduction

Recent studies have reported cognitive dysfunction in schizophrenia patients including measures of attention, information-processing, executive functions, working memory, and verbal fluency. There is increasing evidence that cognitive dysfunction is a more reliable and sensitive predictor of long-term outcome than clinical symptomatology [1]. Deficits in attention and information processing have been considered as a central feature in schizophrenia, which might lead to stimulus overload, cognitive fragmentation and thought disorder [2–7]. Prepulse inhibition (PPI) of the acoustic startle reflex has been proposed as a neurophysiological measure of information-processing abnormalities in schizophrenic patients. The startle reflex is a ubiquitous, cross-species response to an intense and rapid-onset exteroceptive stimulus. It is assessed by measuring the electromyographic response of the orbicularis oculi muscle surrounding the eye in humans. If a weak prepulse precedes a startling stimulus, the response of the startle reflex is reduced (PPI), if the interstimulus interval between prepulse and pulse is longer than 500 ms, then the startle reflex is increased (facilitation). Habituation is the decrement in responding when the same stimulus is presented repeatedly. The PPI- and habituation-paradigms imply that schizophrenic patients show a relative inability to gate intero- and exteroceptive stimuli, which is called deficient sensorimotor gating [8–11]. Schizophrenic patients show a deficit in normal inhibition of the startle reflex with short prepulse intervals (30–150 milliseconds) [10–14]. This deficit of startle inhibition by the prepulse may reflect a biological correlate of sensory flooding and cognitive fragmentation in schizophrenia patients [6, 15]. Specifically, PPI deficits have been shown to correlate positively with thought disorders [4], and positive and negative symptoms [16]. Other studies in schizophrenia found no correlations between clinical ratings and deficits in PPI or habituation [17–19]. It has been demonstrated that the cortical-striatal-pallidal-thalamic circuitry plays a key role in the regulation of PPI [15]. The significant symptom correlations in both positive and negative symptoms have been discussed as the fact that

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the brain substrates regulating prepulse inhibition include those associated with the genesis of both positive and negative symptoms in schizophrenia [16]. PPI is a reliable measure in controls and in schizophrenia patients [20]. PPI deficits are also found at the boundaries of schizophrenia: specifically, in schizotypal disorder [21], psychosis-prone subjects [22], and clinically unaffected relatives of schizophrenia patients [23]. There is some evidence but no controlled study that atypical antipsychotics normalise PPI deficits in schizophrenia [19, 24, 25]. On the other hand Weike et al. found no differences between atypical and typical antipsychotics on PPI in schizophrenia [18].

Previous assessments of habituation in schizophrenic patients have produced somewhat inconsistent results. Some studies showed significant deficits [26–28]. Other experiments assessing habituation in the context of PPI testing have either corroborated these habituation deficits [10, 29] or failed to detect habituation deficits in schizophrenics [16, 20].

One aspect of the complexity of the Schizophrenia phenotype is the fact that it is extremely heterogeneous [30]. This heterogeneity has led a number of investigators to divide the disorder into several subtypes based on clinical psychopathology and course of illness [30–33]. In particular, the distinction between deficit and nondeficit subtype has received both clinical and research interest. Initially, this distinction was conceptualized by Carpenter et al. [34]. Specifically, these investigators divided schizophrenia patients into those with profound and long-term negative symptoms combined with the inability to function independently in society. These patients were characterized as suffering from deficit syndrome schizophrenia. In contrast, those not showing these symptoms and associated impairments were called nondeficit syndrome schizophrenia patients. Thus, the deficit syndrome in schizophrenia defines a subtype with enduring, idiopathic negative symptoms [35]. A 15 year longitudinal follow-up study revealed that nearly one third of the patients developed a deficit syndrome [36]. In subsequent studies, this conceptualization has been further validated. Initially, it was found that neurological signs were associated with the presence of the deficit syndrome [37]. Other studies have shown impaired cognitive performances in deficit versus nondeficit schizophrenia patients [37–39]. Moreover, recent functional neuroimaging investigations support the notion that deficit but not nondeficit schizophrenia patients exhibit prefrontal hypoactivity during memory retrieval [40]. Finally, a study with proton magnetic resonance spectroscopy for the left and right medial prefrontal cortex was performed in schizophrenic patients with deficit and nondeficit syndrome and healthy controls. Lower ratios of N-acetylaspartate to creatine plus phospocreatine suggest a neuronal dysfunction in the frontal region of deficit but not nondeficit patients [41].

If PPI deficits are correlated with negative symptoms [16] and negative symptoms are the enduring characteristic of patients evolving a deficit syndrome, it was hypothesized that the previously observed PPI-deficit is exaggerated in deficit relative to nondeficit syndrome schizophrenia patients. Support for this hypothesis would further validate the distinction between deficit and nondeficit schizophrenia patients. Finally, differential information processing dysfunctions may be used as a phenotypic marker to predict long-term outcome as measured by deficit versus nondeficit status.

To test this hypothesis, schizophrenia patients were recruited from a hospital that provides both short-term and long-term facilities for patients to obtain similar sample sizes of deficit and nondeficit patients according to the Schedule for the Deficit Syndrome [35]. Patients and controls were measured by the startle setup. At the first step all schizophrenia patients were compared to controls; at the second step schizophrenia patients were divided into deficit and nondeficit syndrome forms, these data were compared to controls; at the third step only schizophrenia patients receiving atypical antipsychotics were used for the statistical analyses because different effects between atypical and typical antipsychotics on PPI have been showed [20, 21, 25].

Material and methods

The study protocol was approved by the Psychiatric Services of Aargau Canton Human Subject Committee. Sixty-seven patients with schizophrenia and 44 control subjects were tested. The patients were diagnosed according to the ICD-10 and DSM-IV diagnostic criteria based on an individual semi-structured psychiatric interview performed by an experienced clinician (KL). Additional information was supplied by the treating psychiatrist and by the hospital chart documents. Patients were recruited through the Inpatient Psychiatric Services of Aargau Canton "Klinik Königsfelden" (Switzerland). The catchment area of this psychiatric hospital is the Aargau Canton, a rural district with about 500000 inhabitants. The hospital comprises three facilities: a short-term facility (mean duration of stay about 3–4 weeks, for acute psychiatric crises), a long-term facility, and a geriatric facility (patients >65 years). At the long-term facility, patients are mostly suffering from schizophrenia and are not capable to live without professional psychiatric care. Many of the patients are hospitalised for many years, following long-term rehabilitation some patients are able to live by themselves. For this study we recruited patients both from the short-term and the long-term facilities. The patient group suffering from schizophrenia constisted of 49 men and 18 women. Age-matched controls were hospital employees or were recruited through local advertisements. The con-

trol group included 27 men and 17 women. A semi-structured interview in the control group revealed no personal history of psychiatric disorder, substance abuse, or major medical disorder and confirmed the absence of psychosis in first-degree relatives. Symptoms were rated with the Positive and Negative Syndrome Scale Score (PANSS) [42] and Clinical Global Impression Scale (CGI) [43]. The CGI is an observational scale of global evaluation, it can be applied to any type of patients, regardless of the diagnosis. CGI is a somewhat valid, reliable and widely used instrument [44]. The Positive and Negative Syndrome Scale (PANSS) is the most common psychometric rating scale in schizophrenia, showing good interrater reliabilities, and significant correlations emerged with corresponding criterion measures [45].

Forty-six of the 67 patients with schizophrenia were classified as having deficit syndrome schizophrenia, and 21 were classified as having nondeficit syndrome schizophrenia using the Schedule for the Deficit Syndrome by an experienced clinician (KL) [35]. Demographic characteristics of controls and schizophrenia patients with and without deficit syndrome are presented in table 1, the schizophrenia subgroups differed in age ($T = 3.65$, $p < 0.0005$) and in duration of illness ($T = 3.9$, $p < 0.0003$). Clinical characteristics (PANSS, CGI, age of onset of illness, duration of illness) of schizophrenia with deficit and nondeficit syndrome are presented in table 2. Deficit schizophrenia compared to nondeficit schizophrenia showed higher scores of negative symptoms (PANSS; $T = 2.9$, $p < 0.006$) and higher scores in clinical global impression (CGI; $T = 3.2$, $p < 0.002$). Furthermore, there was a trend towards higher global psychopathology in deficit versus nondeficit schizophrenia (PANSS; $T = 1.8$; $p < 0.07$).

Startle response measurement

Subjects were seated comfortably in an armchair and were instructed to keep their eyes open. The eye-blink component of the acoustic startle response was measured using an EMG startle system (EMG-SR-LAB, San Diego Instruments, Inc., San Diego, CA), with registration parameters as described in detail elsewhere [10]. Two silver/silver-chloride electrodes were placed below the right eye over the orbicularis oculi muscle and a ground electrode was placed behind the right ear. All electrode resistances were less than 5 k□. Acoustic startle stimuli were presented through headphones (TDH-39-P, Maico, San Diego Instruments, Inc., San Diego, CA). Each session began with a 5-min acclimation period of 70-dB background broadband noise that continued throughout the session. The session consisted of 52 trials including two conditions: (1) a 115-dB pulse-alone of 40 ms duration; (2) the same pulse preceded by a 16-dB (above background) prepulse (pp) of 20 ms duration at 30, 60, 120, 240, or 2000 ms (pp 30, pp 60, pp 120, pp 240, pp 2000, respectively). The first and last blocks of a session consisted of 6 pulse-alone trials each that were not used for the calculation of PPI. The middle block of 40 trials consisted of 10 pulse-alone, and 6 of each of the prepulse trials (pp 30, pp 60, pp 120, pp 240, pp 2000) presented in a pseudorandom order. The entire test session lasted about 18 min. All recordings were screened to exclude spontaneous eye-blink activity prior to data analysis, with about 5% of trials being excluded [10].

The startle measures examined were: 1) PPI, percent reduction (%), according to the formula [1– (mean startle magnitude on prepulse (pp 30, pp 60, pp 120, pp 240, or pp 2000) trials / mean startle magnitude on pulse-alone trials (block 2) × 100]; 2) startle magnitudes across blocks 1 to 3, assessing both startle reactivity and habituation uncorrected for differences in response magnitudes; 3) habituation corrected for differences in startle magnitudes, expressed as the percent habituation, according to the formula [1– (mean startle magnitude for block 1 / mean startle block for block 3)].

Statistical analysis

All statistical analyses were performed using STATISTICA/w□ (StatSoft□). PPI- and startle-magnitude-data were analyzed using repeated measures analyses of variance (ANOVA) with trial type (5 prepulse conditions; 3 startle blocks) as within-subject factor, and group (schizophrenia vs. controls; nondeficit schizophrenia vs. deficit

Table 1
Demographic data.

Group	N	mean age	range	SD	males / females
Controls	44	37	20–60	12.2	27 / 17
Schizophrenia (all)	67	39	22–62	10.0	49 / 18
Schizophrenia with deficit syndrome	46	42	26–62	9.7	32 / 14
Schizophrenia with nondeficit syndrome	21	33	22–49	8.0	17 / 4
Schizophrenia with deficit syndrome and atypical antipsychotics	28	44	30–56	8.5	18 / 10
Schizophrenia with nondeficit syndrome and atypical antipsychotics	14	32	22–49	8.0	13 / 1

Table 2
Clinical characteristics.

Positive and Negative Syndrome Scale Score (PANSS)	schizophrenia with deficit syndrome		schizophrenia with nondeficit syndrome		differences (T-test)	
	mean	SD	mean	SD	T	p
Positive symptoms	12.1	6.5	11.1	8.9	0.5	n.s.
Negative symptoms	15.9	5.4	11.1	7.3	2.9	<0.006
Psychopathology	30.2	7.9	25.2	13.4	1.8	(<0.07)
Clinical Global Impression (CGI)	5.3	1.0	4.5	0.8	3.2	<0.002
Age of onset of illness (years)	24.5	6.7	26.4	6.5	1.0	n.s.
Duration of illness (years)	17.3	10.6	5.9	5.1	3.9	<0.0003

schizophrenia vs. controls) as a between-subject factor. Habituation data were analyzed using a one-way ANOVA. Following significant main or interaction effects, planned comparison analyses were conducted with an accepted level of significance of $p < 0.05$.

ANOVA of startle magnitude, habituation, and PPI with subject group (schizophrenia vs. controls) as a between- and 5 prepulse-conditions / 3 startle blocks as a within-factor was performed with data from schizophrenia patients and control subjects. Second, the startle measures obtained from schizophrenia patients were assigned to a patient group with deficit syndrome and a patient group with nondeficit syndrome, respectively. ANOVA with three groups (deficit schizophrenia vs. nondeficit schizophrenia vs. controls) as a between-factor was then performed. Because deficit and nondeficit subgroups were not matched with regard to typical and atypical medication, ANOVA analyses were also performed with patients using atypical neuroleptics only. Finally, in the schizophrenia group Spearman rank correlations between PPI measures and clinical symptoms were calculated.

Results

Detailed statistical results (ANOVA and correlations) are presented in tables 3 and 4, respectively.

Startle magnitude (table 3). Schizophrenia patients did not show differences in startle magnitudes compared to controls, there was also no difference in startle magnitude comparing deficit schizophrenia vs. nondeficit schizophrenia vs. controls. The effect between the three startle magnitude blocks was significant, reflecting the phenomenon of habituation ($F(3, 327) = 204.5$, $p < 0.00001$).

Habituation (table 3). Patients and controls showed similar habituation (% values). This result was unaffected when the schizophrenia group was divided into patients with deficit syndrome and with nondeficit syndrome.

Table 3
Statistical analyses – ANOVA.

Group	measure	Df	F	p
Schizophrenia (all) vs. controls	PPI (see figure 1)			
	group	1, 109	0.8	n.s.
	condition	4, 436	143.05	<0.00001
	group × prepulse condition interaction	4, 436	4.9	<0.00007
	Post-hoc:			
	Pp 60	1, 109	8.5	<0.004
	Pp 2000	1, 109	5.6	<0.02
	habituation group	1, 109	0.1	n.s.
	startle magnitudes group	1, 109	0.8	n.s.
	condition	3, 327	204.5	<0.00001
	group × prepulse condition interaction	3, 327	1.6	n.s.
Schizophrenia with deficit syndrome (sd) vs. schizophrenia with nondeficit syndrome (snd) vs. controls (co)	PPI (see figure 2)			
	group	2, 108	1.7	n.s.
	condition	4, 432	120.8	<0.00001
	group × prepulse condition interaction	8, 432	5.5	<0.00001
	Post-hoc:			
	Pp 240 (sd vs. snd)	1, 108	14.9	<0.0004
	Pp 60 (sd vs. co)	1, 108	8.4	<0.005
	Pp 2000 (sd vs. co)	1, 108	4.6	<0.04
	Pp 240 (snd vs. co)	1, 108	3.2	<0.001
	habituation group	2, 108	0.2	n.s.
	startle magnitudes group	2, 108	0.7	n.s.
	condition	3, 324	176.7	<0.00001
	group × prepulse condition interaction	6, 324	0.9	n.s.
Schizophrenia with deficit syndrome (sd) vs. schizophrenia with nondeficit syndrome (snd) vs. controls (co), medicated with atypical antipsychotics	PPI (see figure 3)			
	group	2, 83	0.5	n.s.
	condition	4, 332	82.3	<0.00001
	group × prepulse condition interaction	8, 332	4.3	<0.00001
	Post-hoc:			
	Pp 240 (sd vs. snd)	1, 83	7.9	<0.006
	Pp 60 (sd vs. co)	1, 83	7.4	<0.008
	Pp 240 (snd vs. co)	1, 83	6.6	<0.01

Figure 1

Comparison of schizophrenia patients (N = 67) and controls (N = 44): Schizophrenia patients showed a significant PPI deficit in the pp 60 ms condition compared to controls (p <0.004) and a reducted facilitation in the pp 2000 ms condition (p <0.02).

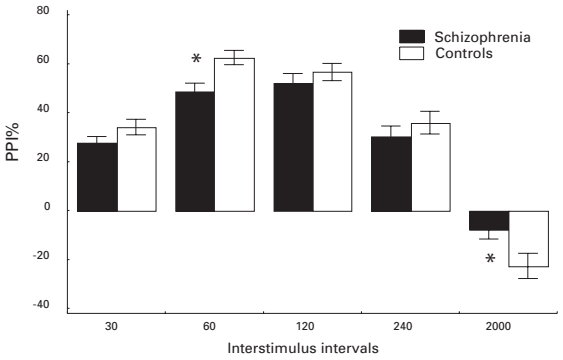

Figure 2

Comparison of schizophrenia with deficit syndrome (N = 46), schizophrenia with nondeficit syndrome (N = 21), and controls (N = 44): The deficit group exhibited significantly reduced PPI in the pp 60 condition (p <0.0004), moreover deficit patients showed reduced facilitation in pp 2000 (p <0.04), whereas patients with nondeficit syndrome showed reduced PPI in pp 240, compared to the deficit syndrome group and to controls (p <0.001).

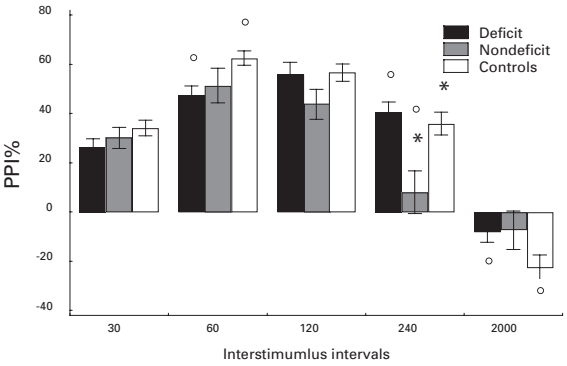

Figure 3

Comparison between deficit (N = 28) and nondeficit schizophrenia (N = 14), only treated with atypical antipsychotics, and controls (N = 44): The increased PPI of PP condition 60 ms in deficit (p <0.006) and of PP condition 240 ms in non deficit schizophrenia (p <0.008) was also seen in patients receiving atypical antipsychotics only.

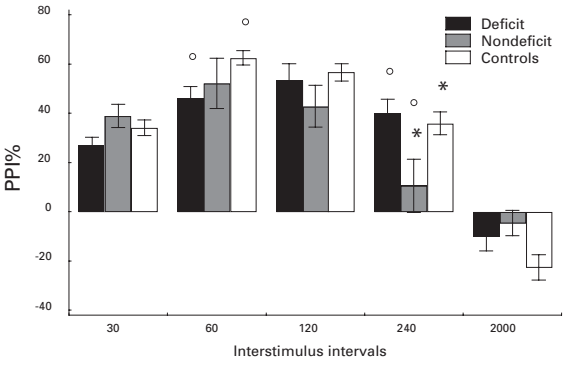

Table 4

Statistical analyses – Spearman rank correlations.

Group	measure	R	t (N-2)	p
All schizophrenia (N = 63)	Pp 60 & negative symptoms (PANSS)	–0.03	–2.1	<0.04
	Pp 60 & Clinical global impression (CGI)	–0.03	–2.2	<0.03

Prepulse inhibition (table 3). Schizophrenia patients showed a significant PPI deficit in pp 60 ($F(1, 109) = 8.5$, p <0.004) and pp 2000 ($F(1, 109) = 5.6$, p <0.02) compared to controls (figure 1). Subgrouped into patients with and without deficit syndrome and compared to controls, this deficit in pp 60 ($F(1, 108) = 14.9$, p <0.0004) was also found in the deficit group; moreover deficit patients showed reduced facilitation in pp 2000 ($F(1, 108) = 3.2$, p <0.04), whereas patients with nondeficit syndrome showed reduced PPI only in pp 240 ($F(1, 109) = 8.5$, p <0.001; figure 2). Impairment of pp inhibition following 60 ms condition in deficit ($F(1, 83) = 7.9$, p <0.006) and pp 240 ($F(1, 83) = 7.4$, p <0.008) in nondeficit schizophrenia was also found following analysis of data from patients receiving atypical antipsychotics only (figure 3). Comparison of the two patient subgroups revealed significant difference in pp 240 ($F(1, 83) = 6.6$, p <0.01; figure 2). The group × prepulse condition interaction ($F(8, 432) = 5.5$, p <0.00001) reflects different PPI-values in the five different interstimulus intervals (pp 30, pp 60, pp 120, pp 240, and pp 2000).

Clinical characteristics and PPI (table 4). PPI prepulse condition 60 ms is negatively correlated with negative symptoms (PANSS; *Spearman* $R = –0.3$, t = –2, 1, P <0.04) and clinical global impression (CGI; *Spearman* $R = –0.3$, t = –2, 2, P <0.03), indicating that patients with higher scores in these psychometric measures showed more deficient PPI following pp condition 60 ms. Due to the limited number of patients (N = 63), this finding has to interpreted cautiously. PPI was neither correlated with chlorpromazine equivalents, nor with age, onset of illness or duration of illness.

Discussion

The present study demonstrates that schizophrenic patients exhibit a significant deficit in the 60 ms prepulse condition but no habituation deficit. This is a replication of previous PPI-studies in schizophrenia [10, 13, 20]. As we hypothesized in an analysis using subgroups, this deficit was found in schizophrenia with deficit syndrome but not in schizophrenia with nondeficit syndrome. Interestingly patients with nondeficit syndrome showed a reduced PPI in the 240 ms prepulse condition. To elude the confounding effect of different antipsychotics, we analysed only patients receiving atypical antipsychotics and got the same result. Previous studies from Kumari and Leumann found differences between atypical and typical antipsychotics in schizophrenia on PPI [19,

24, 25], whereas Weike did not find differences between these medications on PPI [18]. To date there is no controlled pre-post-study investigating the effect of atypical and typical antipsychotics on PPI. More methodological work is needed to clarify these conflicting results.

In accordance with Braff et al. [16] we confirmed the correlation between negative symptoms and PPI. We also revealed a relation between clinical global impression and PPI. Schizophrenia patients with primary and enduring negative symptoms and high severity of their illness showed impaired PPI in pp condition 60 ms. Negative symptoms in schizophrenia have been associated with reduced – especially dopaminergic – frontal activity [40, 41, 46]. Animal models provide evidence that PPI is regulated by frontal cortical dopaminergic substrates [15]. The described PPI deficit in pp condition 60 ms may result from increased frontal dopamine activity. More research is required to explain this finding.

Interestingly, patients with nondeficit syndrome showed a marked PPI deficit in pp 240 ms. Previous studies only investigated pp 30, 60, and 120 ms. This is the first study demonstrating a PPI-deficit in the 240 ms condition in schizophrenia. A previous study with patients suffering from panic disorder found correlations between trait-anxiety and pp condition 240 ms [47]. Based on animal studies the overacitivity of the amygdala has been discussed as being involved in this PPI deficit (pp 240). Recent studies of PPI in different clinical groups will test this hypothesis.

The discovery of a relation between differences in information processing and the presence of deficit or nondeficit syndrome in schizophrenia represents the major finding of this study. Our results are in agreement with a study measuring P300, a different measure of information processing. This study revealed different P300 subcomponent abnormalities in deficit and nondeficit schizophrenia [48]. In contrast to other psychiatric conditions it is possible to differentiate schizophrenia by syndrome levels. However, these ratings appear to be less sensitive to neurobiological correlates [33]. There is a limitation in this study. Deficit syndrome patients were older than nondeficit patients and exhibited a longer duration of illness. However, previous investigations in healthy subjects revealed that PPI is independent of age [49]. We neither found any relation between duration of illness and PPI in our patient sample. The age of onset of illness in our schizophrenia subgroups showed no difference, hence we could not test the hypothesis of Kumari et al., that earlier onset of illness was associated with reduced prepulse inhibition, while adult onset of illness was not [19].

Discrimination between deficit and nondeficit syndrome schizophrenia patients is the first step to determine whether sensorimotor gating dysfunctions are an intermediate phenotype in schizophrenia that can be used to better understand the heterogeneity of this disorder. In accordance with other findings this study supports the hypothesis of two distinct illness subtypes and suggests a neurobiological basis for phenotypic deficit / nondeficit differences. PPI patterns therefore may be useful as subtype markers. Future longitudinal studies will enable us to evaluate whether dysregulation of sensorimotor gating is predictive of future deficit outcome. Another step is to acquire sensitivity and specificity of PPI-deficits with respect to deficit and nondeficit patients. Furthermore a PPI study with deficit and nondeficit schizophrenia combining PPI and imaging (PET/PPI-coregistration) to examine differences in brain activity between these subgroups is ongoing.

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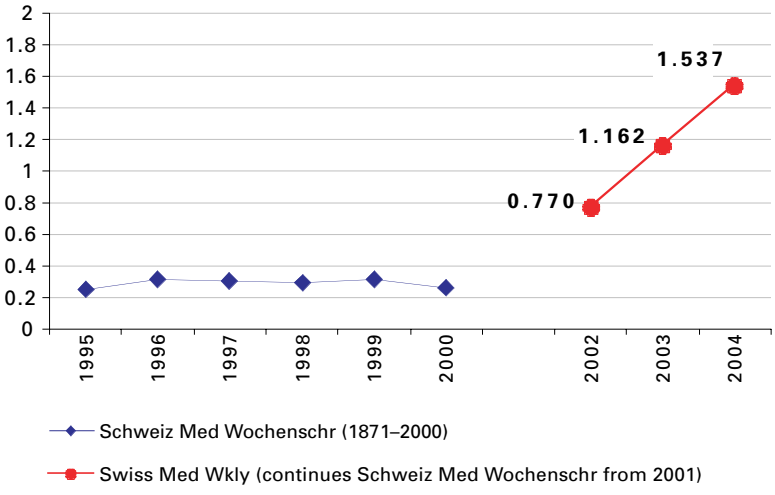

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