Electrophysiological Aberrations Associated with Negative Symptoms in Schizophrenia

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Abstract Clinical heterogeneity is a confound common to all of schizophrenia research. Deficit schizophrenia has been proposed as a homogeneous disease entity within the schizophrenia syndrome. The use of the Schedule for the Deficit Syndrome (SDS) has allowed the definition of a subgroup dominated by persistent and primary negative symptoms. While a number of studies have appeared over the years examining the electrophysiological correlates of the cluster of negative symptoms in schizophrenia, only a few studies have actually focused on the Deficit Syndrome (DS). In this chapter, electrophysiological investigations utilizing EEG, Evoked Potentials (EPs), polysomnography (PSG), or magnetoencephalography (MEG) to probe "negative symptoms," or "Deficit Syndrome" are reviewed. While this line of research is evidently in its infancy, two significant trends emerge. First, spectral EEG studies link increased slow wave activity during wakefulness to the prevalence of negative symptoms. Second, sleep studies point to an association between decrease in slow wave sleep and prevalence of negative symptoms. Several studies also indicate a relationship of negative symptoms with reduced alpha activity. A host of other abnormalities including sensory gating and P300 attenuation are less consistently reported. Three studies specifically

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addressed electrophysiology of the DS. Two of the three studies provided evidence suggesting that the DS may be a separate disease entity and not simply a severe form of schizophrenia.

Keywords Deficit syndrome · Negative symptoms · Schizophrenia · Evoked potentials (EPs) · Electroencephalography (EEG) · Polysomnography (PSG)

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1 Introduction

Enduring negative symptoms in patients with chronic schizophrenia correlate with decreased functional outcome (Tandon et al. 2000; Buchanan 2007; Green 2006; Kirkpatrick et al. 2006) and are refractory to common pharmacological interventions (Buchanan 2007; Buchanan et al. 2007; Galderisi and Maj 2009). It has long been recognized that negative symptoms can be secondary to medication effects, co-morbid mood disorders, or even resulting from significant cognitive disorganization. The development of the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al. 1989) has allowed the definition of a subgroup of schizophrenia patients dominated by clusters of primary and enduring negative symptoms (Kirkpatrick et al. 1989). This subgroup of patients (deficit schizophrenia, DS) arguably suffers from the most severe and costly form of all of the subgroups of schizophrenia (Galderisi and Maj 2009; Kirkpatrick and Galderisi 2008).

Functional or anatomical probing of individual psychiatric symptoms or symptom clusters within a psychiatric syndrome is a relatively recent endeavor. Schizophrenia symptomatology varies widely affecting the cognitive, affective, and reality testing domains. Three sets of symptoms received particular attention: positive, negative, and cognition-related symptoms. Based on the fundamental

differences and likely brain structures involved in the generation of these symptom clusters, an assumption can be made that the underlying physiopathologies mediating these symptoms are different. Neuropathological findings associated with schizophrenia in general have implicated most of brain structures but with significant emphasis on frontal, temporal, and thalamic regions. While the complete understanding of the pathophysiology of the DS is not possible with the current level of knowledge, most studies suggest pervasive bottom-up deficiencies that may lead to cascading information processing problems. This tentative conclusion is based on the observation that information processing abnormalities gleaned from evoked potentials (EPs) studies tend to occur earlier in the sequence of EPs and starting during periods that are commonly considered as "pre-attentive."

Significant efforts are now being expended in attempting to ascertain whether DS is a subgroup of schizophrenia with identified abnormalities proving to be only quantitative and not qualitatively different from rest of schizophrenia subgroups. On the other hand, it is suggested that if identified abnormalities closely associated with the DS are qualitatively different then it would be possible to postulate DS as a separate psychopathological entity. The clear demarcation of the DS and its early identification could lead to better treatment and rehabilitation efforts.

Electrophysiological investigations, including electroencephalography (EEG), magnetoencephalography (MEG), evoked potentials (EPs), and sleep studies represent investigative methodology that can assess chronology at a millisecond by millisecond level of the information processing cascade in the intact behaving human. Research utilizing this methodology has pointed out to a number of highly replicable physiological aberrations in individuals suffering from schizophrenia. None the less, no biological abnormality has proven to be diagnostic or even present in a significant majority of patients. One reason commonly advanced for such is the agreed upon heterogeneity of the syndrome. By identifying the aberrations that are more specifically linked to a particular symptom (e.g., hallucination) or to a symptom cluster (positive, negative or cognitive), advances can be made toward better understanding of the neural circuitries subserving different symptom clusters, as well as the disorder as a whole. Defining the electrophysiological changes most closely linked to negative symptoms may allow guided research to probe specific negative symptoms like avolition and emotional blunting.

Physiological probing of brain function and dysfunction uses two fundamentally different technologies; functional (as contrasted to structural) neuroimaging and electrophysiology. While neuroimaging has superior spatial resolution, electrophysiology enjoys a superior temporal resolution. It is widely agreed upon that the two methodologies are complementary (Boutros et al. 2011) and efforts are underway for the simultaneous recording of both kinds of brain activity. In this review, we focus on electrophysiological investigations probing negative symptoms or the deficit syndrome and attempt to leverage the existing electrophysiology literature in schizophrenia in an attempt to investigate the possibility of a unifying hypothesis for the pathophysiology of negative symptom in schizophrenia patients. A testable hypothesis is whether positive symptoms represent a more

localized dysfunction in the frontotemporal-thalamo-striatal-cortical circuitry while negative symptoms (and more fully the DS) may be secondary to a more widespread cortical-thalamo-striatal-cortical dysfunction. It is also quite possible that the nature of involvement of the frontal cortex is different in groups of schizophrenia patients with predominance of negative, positive, or cognitive dysfunctions.

2 EEG Changes in Association with Negative Symptoms

EEG abnormalities in schizophrenia have been noted since the early days of electroencephalography. The emergence of the ability to analyze EEG signals with the aid of the computer allowed the intense and detailed interrogation of the rich electrophysiological data. An increase of slow activity in the delta and theta range (1–8 Hz) was consistently reported in schizophrenia (Galderisi and Maj 2009). Spectral EEG studies have linked increased slow wave activity to the prevalence of negative symptoms (Boutros et al. 2008a).

Table 1 lists studies that directly addressed the correlation between negative symptoms and/or the deficit syndrome EEG changes. Table 1 also highlights the varying EEG methodologies used in probing negative symptoms (and schizophrenia in general) (Boutros et al. 2008a). Totally, 5 of the 11 studies using spectral analysis point to an increased slow activity (mainly theta rhythms of 4–8 Hz frequency) in association with negative symptoms. A relatively recent study supported the observation of a significant correlation between increased theta activity and negative symptoms (Venables et al. 2009). In this study the strongest correlations were obtained from frontal, central, and occipital regions while correlation between EEG data obtained from temporal regions and negative symptoms barely reached significance. This observation suggests that the increased theta seen in association with negative symptoms may be more represented in certain brain regions and may have significant implications to the eventual identification of the specific circuitry underlying the development of these symptoms (Venables et al. 2009). These findings also underline the possibility that the pathophysiology associated with negative symptoms may be widespread. The computational role of theta oscillation has been linked to periodic modulation of synaptic transmission and plasticity (Lengyel et al. 2005). Persistent theta neural activity lasting for seconds after transient stimulation has been observed in several brain regions. This activity has been taken to be indicative of the integration of inputs on long time scales (Huhn et al. 2005).

As far as delta band activities are concerned, some studies have found enhanced delta band activity in the prefrontal cortex in neuroleptic-naïve subjects with schizophrenia (Pascual-Marqui et al. 1999) or a generalized increase in delta band activity, most prominently in the anterior cingulate gyrus and temporal lobes (Mientus et al. 2002). Itoh et al. (2011) conducted the first study to assess, in first episode drug-naïve patients, if delta band activity would be increased in brain

Table 1 EEG studies examining correlation with negative symptoms

Study	Sample	Assessment	Measurement	Findings
Williamson et al. 1989[a]	20 Sch 20 HC	DSM-IIIR SCID	Spectral EEG resting and during WCST	Neg Sx correlate with smaller increase in beta during WCST
Kessler et al. (1991)	18 Sch (med free) 13 HC.	DSM-IIIR Diagnostic Interview Schedule	Spectral EEG with auditory emotionally salient and control stimuli	Residual/Undifferentiated subgroup with predominant neg Sx showed more beta1 and less alpha at temporal sites and more beta1 and beta2 at frontal sites versus controls; they had different lateralization patterns in the delta band after emotionally salient stimuli
Merrin and Floyd (1996)[b]	17 Sch (med free (14 days)	DSM-IIIR by the SADS, BPRS	Spectral EEG	Reduced alpha power, decreased alpha coherence between hemispheres associated with neg Sx
Sponheim et al. (1997)	28 Sch (winter born) 81 Sc3h (non-winter born) 18 non-sch psychosis	PSE, DSM III	Nonwinter born CS and non-schizophrenia	This paper strongly documents heterogeneity within schizophrenia groups. Psychotic patients had increased low frequency and decreased alpha power. Winter born Sch and non-schizophrenia psychotic patients had no power abnormalities
Sponheim et al. (2000)[b]	112 Sch, 78 psychotic not sch, 107 controls	PSE DSM-IV	EEG spectral, relative, only Cz data examined	Low alpha—high slow activity factor scores associated with negative Sx in Sch patients
Knott et al. (2000)[a]	17 Sch, free of neuroleptics	DSM-IIIR, clinical, PANSS	EEG spectral analysis, intra, and interhemispheric coherence	No clear correlate of neg Sx pre clozapine Tr. Greater interhemispheric theta and beta asymmetry predicted good response in both pos and neg Sx. Greater intrahemispheric delta asymmetry predicted response of neg Sx

(continued)

Table 1 (continued)

Study	Sample	Assessment	Measurement	Findings
Winterer et al. (2000)	Two trainer (33 Sch, 49 Con), and a test set (32 Sch, 49 HC)	ICD-10 clinical interview	EEG spectral resting and activated and auditory evoked responses	Patients with predominantly negative symptoms were more readily classifiable based on frontally pronounced delta activity and decreased power of the N100/P200 evoked response
Strelets et al. (2002)[b]	Only male subjects. Pos Sx Sch 16 Neg Sx Sch 20, 16 HC	DSM-IIIR clinical interview	High frequency oscillation connectivity	Decreased connectivity between frontal regions in neg Sx patients
Fehr et al. (2003)[a]	Sch 30 (9 unmedicated),17 HC	DSM-IV Clin Int, PANSS	MEG, spectral analysis	Relative % of slow activity in temporal regions corr with neg Sx
Manchanda et al. (2008)[a]	117 first episode psychosis	SCID-IV, SAPS, SANS	Standard (visually inspected) EEG (sEEG)	Pretreatment sEEG abnormalities predict poorer response of both positive and neg Sx
Venables et al. (2009)[a]	Sch 48 (medicated), 61 1st-degree relatives	25-item BPRS	Spectral analysis	Increased theta activity during eyes closed condition in Sch
Itoh et al. (2011)	Sch 17 first episode drug-naïve 17 HC	SCID, SAPS, SANS	Delta band activity, using LORETA current density	LORETA values for delta band activity in left inferior temporal gyrus, right middle frontal gyrus, right superior frontal gyrus, right inferior frontal gyrus, and right parahippocampal gyrus. were negatively correlated with negative, but not positive symptoms
Noh et al. (2013)	15 Sch with chronic schizophrenia 17 HC	DSM-IV PANSS	MEG, spectral analysis	CLGFcircuits in the cortical functional network are related to the abnormal synchronization and correlated to the negative symptom

Applicability to the DS [a] Possibly applicable
[b] *Likely applicable* description clear
[c] Description inadequate for a determination
Sx Symptoms, *PSE* Present State Exam, *sEEG* Standard visually inspected EEG

areas with a relevant relationship with the pathophysiology of schizophrenia and its correlation with the symptomatology of schizophrenia (e.g., positive and negative symptoms). Low Resolution Brain Electromagnetic Tomography (LORETA) was used to generate current source density images of delta, theta, alpha, and beta activities and localize the difference in EEG activity between patients and healthy controls. Current density for delta band activity was greater for patients in the left inferior temporal gyrus, right middle frontal gyrus, right superior frontal gyrus, right inferior frontal gyrus, and right parahippocampal gyrus. Current density values for delta band at these brain regions showed a negative correlation with the Scale for Assessment of Negative Symptoms (SANS) total score and no significant correlation with Scale for Assessment of Positive Symptoms (SAPS) score. The results of this study indicated that increased slow activity in frontal regions is not associated with positive symptoms and is more marked in subjects with fewer negative symptoms. In the light of recent conceptualization of increased delta band over frontal regions as an electrophysiological sign of reduced attention to the external input, the authors hypothesized that subjects with increased frontal delta may be able to reduce external input, cope better with positive symptoms and have less secondary negative symptoms. It is thus clear that further research is needed to more fully understand the interrelationship between increased slow wave activity, particularly in the frontal regions, and schizophrenia symptomatology.

A less consistently reported abnormality is altered reactivity and/or predominance of faster rhythms (beta activity). Noh et al. (2013) analyzed magnetoencephalography (MEG) data in chronic patients with schizophrenia and found reduced gamma power and increased beta band synchronization. Using an index of intra and interregional cortical functional connectivity (the amount of coupled local and global feedback (CLGF) circuits) they found that dysfunctional connectivity was related to the abnormal synchronization of the beta band and to negative symptoms.

Another important approach of describing dynamical systems is nonlinear analysis, called chaos theory, which allows researchers to determine changes in the dimensionality of the system over time (Kotini and Anninos 2002). A higher rate of phase-state transitions (i.e., higher dimensionality) characterizes more complex systems. Earlier work revealed that nonlinearity scores were significantly lower during awake state in schizophrenia patients compared to control subjects suggesting that there may be diminished interplay between different generators of the various EEG rhythms (Keshavan et al. 2004). Decreased nonlinear complexity correlated with neurocognitive deficits. Other groups found an increase in the dimensional complexity in schizophrenia patients (Koukkou et al. 1993; Rockstroh et al. 1997). Kotini and Anninos (2002) when using MEG to examine nonlinearity in schizophrenia patients also reported lower dimensional complexity. One possible contributor to the discrepancy is heterogeneity of study samples. A readily testable hypothesis would be that decreased dimensionality would correlate with increased cognitive deficit and possibly negative symptoms.

Yet another recently evolving methodology is to stimulate the cortex using transcranial magnetic stimulation (TMS) and examine the resultant EEG effects. While yet to be applied specifically to probe the deficit syndrome, Guller et al. (2012) used this methodology to test the hypothesis that direct physiological stimulation of the cortex will produce an abnormal thalamic response in individuals with schizophrenia. They stimulated the precentral gyrus with single pulse TMS (spTMS) and measured the response to this pulse in synaptically connected regions (thalamus, medial superior frontal cortex, insula) using concurrent functional magnetic resonance imaging. Compared with healthy subjects, patients with schizophrenia showed a reduced response to spTMS in the thalamus, medial superior frontal cortex, and in the insula. Functional connectivity analyses revealed weaker thalamus–medial superior frontal cortex and thalamus–insula connectivity in patients with schizophrenia compared with control subjects. Subsequently, the same group utilized the same technology probing EEG effects to assess the natural frequency of the posterior parietal, motor, premotor, and prefrontal cortices in patients with schizophrenia and healthy control subjects. High-density EEG recordings during TMS of four cortical areas were performed. Several TMS-evoked EEG oscillation parameters, including synchronization, amplitude, and natural frequency, were compared between the schizophrenia and control groups. Patients with schizophrenia showed a slowing in the natural frequency of the frontal/prefrontal regions compared with control subjects (from an average of a 2-Hz decrease for the motor area to an almost 10-Hz decrease for the prefrontal cortex). The prefrontal natural frequency of individuals with schizophrenia was slower than in any healthy comparison subject and correlated with both positive and negative syndrome scale scores suggesting that these abnormalities may be common between patients dominated by positive or negative symptoms and further implicates thalamic abnormalities in schizophrenia. It could be speculated that frontothalamo-striatal-frontal circuit dysfunctions are common to all schizophrenia patients and perhaps contributing to the common coexistence of the varying manifestations of the disorder. According to our hypothesis advanced above, the development of a DS picture may require involvement of other cortical regions beyond frontal and perhaps temporal regions.

3 Evoked Potentials (EP) Changes Associated with Negative Symptoms

Disturbances in sensory processing have been suggested as significant contributors to the deficit state in both clinical and neurophysiological studies (Turetsky et al. 1998; Mucci et al. 2007; Li et al. 2013). Two studies have thus far demonstrated qualitative differences between DS and NDS (nondeficit) patients utilizing EP measures (Turetsky et al. 1998; Mucci et al. 2007). Thus, surrogate markers of sensory information processing are promising tools for probing the pathophysiology

of the DS as well as delineating differences between DS and NDS physiological aberrations. Table 2 lists studies that directly examined the correlation between negative symptoms and evoked potential changes.

3.1 Mid-Latency Auditory Evoked Responses and Sensory Gating

The mid-latency auditory evoked responses (MLAERs) have been extensively used to study information processing both in mental health and disease. Numerous studies have shown two particular components to be abnormally reduced in amplitude in patients with schizophrenia. These two components are the N100 (a negative component seen approximately 100 ms following an auditory stimulus) and the P50 (a positive component seen about 50 ms after the presentation of an auditory stimulus) (Erwin et al. 1991). The N100 component has been extensively examined in schizophrenia patients. The majority of studies report decreased amplitude of the N100 which is not readily attributable to medication effects (Rosburg et al. 2008). N100 amplitude is commonly (but not invariably) found to be reduced in patients with schizophrenia (Rosburg et al. 2008) and in unaffected first-degree relatives of the same patients (Ahveninen et al. 2006). The relationship between N100 amplitude and specific schizophrenia symptoms remains unclear (Rosburg et al. 2008).

The P50 MLAER has also been used extensively to examine the phenomenon of amplitude attenuation with stimulus repetition. The term "sensory gating" has been linked with studies of sensory inhibition utilizing the P50 MLAER in a paired stimulus paradigm (PSP). Abnormal sensory gating has been proposed as a fundamental mechanism by which psychotic symptoms evolve (Freedman et al. 1991). In a PSP, two identical stimuli (S1 and S2) are delivered with short interstimulus interval of 500 ms and a longer interpair interval of 8–10 s (Adler et al. 1982). A sensory gating deficit has been repeatedly demonstrated in schizophrenia patients (Adler et al. 1982; Boutros et al. 1991). Meta-analysis of the P50 gating deficit in groups of nonselective schizophrenia, patients found the effect size to be more modest than earlier reports suggested (Patterson et al. 2008). Heterogeneity of both methodology and composition of patient groups were suggested as possible causes for variation in results. A number of studies suggest that the gating deficit, particularly of the N100 component, may be more strongly found in association with negative symptoms (Boutros et al. 2009).

The gating deficit as assessed by the P50 component was examined in relationship to negative symptoms and was not found to correlate with any symptom cluster in earlier studies (Adler et al. 1990; Boutros et al. 2004). Subsequent investigations of gating of the P50 MLAER component reported a significant correlation with negative symptoms (Ringel et al. 2004; Louchart-de la Chapelle et al. 2005; Arnfred 2006). More recently Santos et al. (2010) investigated P50

Table 2 EPs

Study	Sample	Measurement	Assessment	Findings
Pfefferbaum et al. (1989)	31 Sch 37 HC	P300 amplitude	BPRS	P3 smaller in patients with a pos correlation with neg Sx in unmedicated patients
Adler et al. (1990)[a]	20 medicated (9 predominantly negative) Sch, 12 control	P50 gating		No correlation of P50 gating and negative symptoms
Boutros et al. (1991)[a]	13 medicated nonparanoid, 13 paranoid, Sch, and 13 control	P50 amplitude and gating	BPRS	P50 amp and gating decreased in nonparanoid patients
Boutros et al. (1993)[a]	13 paranoid Sch 11 nonparanoid (all unmedicated) 11HC	P50 amplitude	DSM-3-R clinical interview	P50 amp decreased in nonparanoid patients
Turetsky et al. (1998)[b]	65 Sch (30 un-medicated), 48 HC	P300	BPRS, SANS, SAPS	Asymmetrical P3 reduction only in NDS while DS patients had reduction in r-Parietal
Baldeweg et al. (2002)	Medicated Sch (N=14), control (N=14)	Duration MMN	ICD-10 (clinical interview, Manchester Scale, Digit span, verbal fluency	No correlations with symptoms clusters
Jeon and Polich (2003)	Literature review	P300	NA	No overall correlation with neg Sx but a strong negative correlation with paranoid symptoms
Boutros et al. (2004)	Medicated Sch (atypical neuroleptics) 23 cont, 23	P50 gating	PANSS	No relationship between P50 gating and neg Sx
Ringel (2004)	34 Sch (medicated) 12 HC	P50 gating	PANSS	P50 gating corr + with neg Sx

(continued)

Table 2 (continued)

Study	Sample	Measurement	Assessment	Findings
Louchart-de La Chapell (2005)	81 Sch (medicated) 88 HC	P50 gating and P50 latency	SAPS and SANS	P50 gating dec in gen but more in assoc with neg Sx
Thoma et al. (2005)[b]	20 Sch (medicated)	P50 EP and MEG gating	SCID for DSM-IV, SANS, PANSS	No relationship between P50 (EP) gating and neg Sx. Right hemisphere M50 (MEG) gating ratios positively correlated with neg Sx (worse gating-more neg Sx)
Arnfred (2006)[b]	17 Sch spectrum (unmedicated), 24 HC	P50 EP and P50 Gating	SANS and SAPS	Difference wave calculated by subtracting S2 wave from S1 wave. Decreased P50 amplitude and difference wave in patients with severe negative Sx
Toyomaki et al. (2008)[c]	23 Sch (medicated)	Duration MMN	SCID and WCST	Strong correlation between MMN amplitude and executive functioning
Mucci et al. (2007)[b]	Sch (medicated) (DS = 20), non-DS = 20, and HC = 20	N100 and P300	SANS/SAPS and EBPRS	Double dissociation:N100 small in DS and P300 small in non-DS
Boutros et al. (2009)[a]	45 Sch (medicated), 49 HC	P50, N100, P200 gating	PANSS	N100 gating deficit correlates with negative symptoms
Santos et al. 2010[b]	60 DS, 60 NDS, 60 HC	P50 gating	SDS	No correlation to negative or positive symptoms but patients in general had worse gating which corr with poor outcome
Olincy et al. (2010)	181 Sch (medicated), HC 333	P50 gating	SCID and SANS/PANS	P50 gating decreased in group in general but no corr with clinical clusters

(continued)

Table 2 (continued)

Study	Sample	Measurement	Assessment	Findings
Smucny (2013)	21 Sch 23 HC	Sensory gating at the beta and gamma frequencies	DSM-IV BPRS SANS	Poor beta gating was associated with negative symptoms
Wynn et al. (2010)	34 Sch 36 HC	CNV SPN	SCID I BPRS SANS TEPS Social anhedonia scale Physical anhedonia scale	Patients demonstrated generally lower CNV and SPN across pleasant, neutral, and unpleasant picture conditions without a relationship with clinical symptomatology and anhedonia
Horan et al. (2012)	35 Sch 33 HC	FN ERN	SCID I BPRS	Patients and controls demonstrated comparable FN differentiation between reward and nonreward condition, and no correlation between negative symptoms and FN
Li et al. (2013)	21 DS, 38 NDS, 50 HC	P300 (P3a and P3b), MMN, P50 amp and gating, CNV		DS patients showed delayed point A in CNV which correlated with poorer Global assessment of Functioning scale but not with any individual negative symptom
Wysse (2013)	13 neg Sx Sch and 13 HC	LDAEP N1/P2		LDAEP in the right hemisphere in patients was related to higher scores in scales assessing negative symptoms

[a] Possibly applicable
[b] *Likely applicable* description clear
[c] Description inadequate for a determination
LDAEP Loudness dependence of auditory evoked potentials; *CNV* Contingent negative variation

gating in patients with DS and in those with nondeficit schizophrenia (NDS). These authors did not find differences in P50 gating between the two groups of patients, but found an association between the abnormality of P50 gating and poor functional outcome. These contradictory findings suggest that the relationship between primary, enduring negative symptoms and the P50 gating deficit are not simple or straightforward and may depend strongly on the specific composition of the study sample. Given the documented high prevalence of smoking among schizophrenia patients it is also important to control for smoking status of the patient and the time elapsed between the last cigarette and P50 testing as transient improvement in P50 gating following nicotine/cigarette smoking has been demonstrated (Leonard et al. 2007). It is also possible that the effect size of the observation is not robust enough to be detected in smaller samples or in the presence of a high noise to signal ratio as is common in P50 studies due to the relative small amplitude of the component (Boutros et al. 2009). Furthermore, the specific scale or instrument used to assess the negative symptoms (or for that matter any symptom cluster) may also influence the correlations identified (Boutros et al. 2009). An alternative hypothesis is that a mediating variable (not as yet identified), cross-correlated with negative symptoms and gating deficits (e.g., poor outcome), is responsible for the association between P50 gating deficit and negative symptoms. Further studies are needed to clarify the issue.

Evidence for a frontal cortex role in mediating both auditory and somatosensory habituation has been provided by MEG studies (Bowyer et al. 2007; Weiland et al. 2008), EEG studies (Korzyukov et al. 2007; Garcia-Rill et al. 2008) and from direct brain recordings (Grunwald et al. 2003; Boutros et al. 2008a, b). Physiological data have indicated that the inability to suppress irrelevant inputs, coupled with difficulty in novelty detection (which may be related and indexed here by the MMN), impairs the coding at the beginning and ending of discrete events. Information is stored with incorrect spatiotemporal tags (Knight et al. 1995). A number of studies documented a working memory deficit in schizophrenia patients (Goldman-Rakic 1999). It has further been postulated that it is the inability to gate irrelevant information during the recall period, that causes the deficit to become manifest. Chao and Knight (1995) tested this hypothesis in a number of patients with dorsolateral prefrontal cortex (DLPFC), temporal–parietal junction (TPJ), or posterior hippocampus lesions. They showed that patients with prefrontal lesions were significantly impaired by distractors at all delays while patients with temporo-parietal lesions performed similar to control subjects. Individuals with DLPFC lesions exhibited increased amplitudes of the mid-latency auditory evoked responses (MLAERs) beginning 25–35 ms following auditory stimulation (Knight et al. 1989). It is possible to speculate that the preattentive gating abnormality (mediated by the P50) may be common to all schizophrenias while the later occurring (or early attentive) gating abnormalities (reflected by either the N100 or the P200 EPs) may be more linked to negative symptoms (also a readily testable hypothesis).

Smucny et al. (2013) most recently used time–frequency analysis to compare sensory gating at the beta (15–26 Hz) and gamma (30–50 Hz) frequencies

between schizophrenia patients and healthy controls. Relative to controls, patients showed impaired gating of total beta and gamma power. Poor beta gating was associated with negative symptoms. Time–frequency analysis of beta and gamma gating may thus be a translational method of assessing the genetic basis of gating deficits in schizophrenia.

3.2 Mismatch Negativity

The mismatch negativity (MMN) is an early EP (with latency around 150 ms from the stimuli onset) related to automatic probing of auditory sensory traces of a repetitious stimulus by a deviant one elicited in an oddball paradigm (Näätänen et al. 1978; Sams et al. 1985). MMN is considered a preattentive process and thus mainly a bottom-up function. While MMN has been shown to be diminished in a number of studies of schizophrenia patients, not all studies find similar deviations (some find duration and others find frequency deviation MMN alterations). We propose that one possible explanation of the variance in the findings is related to inclusion of different patient samples and not paying specific attention to negative versus positive symptoms as well as not paying attention to enduring primary negative versus secondary negative symptoms. The MMN has not yet been specifically investigated in well-characterized DS patients. Based on the assumption that DS patients suffer from an early (preattentive and bottom-up) sensory processing deficit, we fully expect that future MMN investigation will reveal abnormalities of this component in DS patients. At the time of preparing this chapter, only a relationship between diminished frequency MMN and executive dysfunction has been reported (Toyomaki et al. 2008).

3.3 The P300

The P300 response is a positive deflection appearing around 300 ms from stimuli onset in response to rare novel or deviant stimuli in an auditory oddball paradigm. Its amplitude is proportional with the amount of attentional resources allocated to the task and memory performance (Polich 2007). The P300 as well as the MMN have been found to be abnormally small (and sometimes delayed) in schizophrenia populations (Javitt et al. 1993; Näätänen and Kähkönen 2009; Jeon and Polich 2003; Gjini et al. 2010). The P300 response represents processing of information at more advanced cognitive levels, such as a shift of attention, context updating, or orienting to a relatively novel or deviant stimulus (Polich and Kok 1995). Examination of the P300 is of particular importance as evidence suggests that it may be relatively spared in DS patients (Mucci et al. 2007; Jeon and Polish 2003). It is of importance to note that a meta-analysis of the P300 ERP in schizophrenia found a correlation with positive but not negative symptoms (Jeon and Polish 2003).

Mucci et al. (2007) were able to corroborate this finding in a group of well-characterized DS patients. Confirmation of this important observation would significantly contribute to the delineation of the neural circuitry implicated in DS. Engagement of frontal attention mechanisms during evaluation of novel incoming stimuli produces the P3a response with a midline centrofrontal maximum as compared to the classic P300 (i.e., P3b) activity to attended target stimuli showing a midline parietal maximum and has been related to context updating operations and subsequent memory storage (Polich 2007). A recent fMRI study (Wolf et al. 2008) showed a negative correlation of novelty-induced BOLD signal in the left frontal cortex with SANS scores, indicating lower levels of activation in patients with more severe negative symptoms. No significant correlations were identified for novel-induced BOLD signal and positive symptoms; also no significant correlations for target-induced BOLD with either positive or negative symptoms. Based on the limited available literature examining the correlations between P3 and negative symptoms we predict that DS patients will exhibit deficit in the ability to respond to novelty reflected by generating lower amplitude P3a components, but preserved target P300 (P3b).

Kim et al. (2013) analyzed four event-related potential (ERP) components (P100, N170, N250, and P300) and their source activities using EEG data acquired from 23 schizophrenia patients while they were presented with facial emotion picture stimuli. Correlations between positive and negative syndrome scale (PANSS) scores and source activations during facial emotion processing were calculated to identify the brain areas affected by symptom scores. Analysis demonstrated that PANSS positive scores were negatively correlated with major areas of the left temporal lobule for early ERP components (P100, N170) and with the right middle frontal lobule for a later component (N250), which indicates that positive symptoms affect both early face processing and facial emotion processing. On the other hand, PANSS negative scores were negatively correlated with several clustered regions, including the left fusiform gyrus (at P100), most of which are not overlapped with regions showing correlations with PANSS positive scores. These recent results suggest that positive and negative symptoms affect independent brain regions during facial emotion processing.

3.4 Error-Related and Correct-Response Negativity (ERN and CRN)

Deficits in self monitoring are a core feature of cognitive dysfunction in schizophrenia, and may be the basis for disturbances of self and lack of insight, ultimately impacting social functioning. DS patients are characterized by a significant lack of insight. However, the functional and structural neural correlates of such deficits in self monitoring are not well understood (Araki et al. 2013). This group of researchers investigated this issue using measurements of neurophysiological

and structural brain indices, i.e., error-related and correct-response negativity (ERN and CRN) ERPs, and gray matter volume of the anterior cingulate cortex (ACC), and tested whether the association between these indices is altered in patients with schizophrenia compared to healthy controls. The two groups did not differ in ERN amplitude. In contrast, schizophrenia patients showed significantly larger CRN amplitudes than did healthy subjects. Although the two groups did not significantly differ in gray matter volume of the ACC subregions, a significant negative correlation was found between ERN amplitudes at the frontocentral electrodes and absolute gray matter volumes of the left region of ACC only in healthy controls. These results suggest a disruption of function–structure coupling of the brain regions subserving self monitoring in schizophrenia. A direct comparison between DS and non-DS schizophrenia patients would be informative in this regards.

3.5 Anticipatory Components: Contingent Negative Variation (CNV) and Stimulus-Preceding Negativity (SPN)

The negative symptoms construct has been refined with the modern conceptualization identifying 5 core component that have been shown to separate into two domains: 1) a motivational dimension consisting of anhedonia, avolition, and asocialty and 2) a diminished expressivity dimension consisting of restricted affect and alogia (Strauss et al. 2013). In schizophrenia reward deficits involve more than just anhedonia (Foussias and Remington 2010). In some cases, while the ability to experience pleasure may even remain intact, patients with schizophrenia more consistently demonstrate an impaired anticipation of reward, not immediately available (Gold et al. 2008) and impairments in several other facets of reward processing involved in motivation (Strauss et al. 2013).

ERP components studied in relation to anticipation of reward include the contingent negative variation (CNV), a slow negative brain wave shown to reflect the anticipation of or orienting to the upcoming stimulus and response preparation, and has been related to preparatory attention, motivation, and response readiness (Walter et al. 1964), and the stimulus-preceding negativity (SPN), a negative ERP detected in paradigms that involve anticipation of feedback about the correctness of prior performance or stimuli that are motivationally significant (van Boxtel and Bocker 2004). Schevernels et al. (2014) showed that reward anticipation was linked to early cue processing components, as well as the early and later parts of the CNV. Wynn et al. (2010) investigated anticipatory deficits in subjects with schizophrenia in a paradigm involving a cued motor response (CNV) and no motor response (SPN) and the relationships of these ERP components abnormalities with self-reported trait anhedonia or anticipatory pleasure and clinically rated negative symptoms. Patients demonstrated generally lower CNV and SPN across pleasant,

neutral, and unpleasant conditions; SANS total score did not correlate with the ERP variables; higher trait anhedonia was related at a trend-level to lower overall SPN.

Other facets of motivation found to be impaired in schizophrenia include difficulties using internal representations of emotional experiences, previous rewards, and motivational goals to drive current and future behavior, deficits that have major clinical significance in terms of functional capacity (Barch and Dowd 2010). The feedback-related negativity (FRN) is an ERP component that has been localized to the ACC (Nieuwenhuis et al. 2005) and has been hypothesized to reflect the function of a performance monitoring/evaluative system that rapidly assesses the motivational impact and/or salience of environmental feedback (Segalowitz et al. 2010). Fitting this view, the FRN has been found to be sensitive to both errors in reward prediction, negative valence of emotional stimuli (Pfabigan et al. 2011) and the magnitude of outcome (Holroyd and Krigolson 2007; Holroyd et al. 2004). In their study, Horan et al. (2012) tried to clarify the scope of feedback processing impairments in schizophrenia analyzing FRN during a simple monetary gambling task. The authors also investigated the relationships between FRN abnormalities and negative symptoms, assessed using the BPRS. They showed that patients and controls demonstrated comparable FRN differentiation between reward and nonreward feedback and higher positive symptoms were associated with greater differences between FRN to positive and negative feedback. There were no significant or trend-level correlations for negative symptoms. In their opinion the use of the BPRS may have limited ability to detect an association between negative symptoms and reward processing because the BPRS negative symptom subscale focuses on expressive symptoms (e.g., blunted affect) whereas experience-related symptoms (e.g., avolition, asociality) have a stronger theoretical link to feedback and reward processing (Blanchard et al. 2011).

3.6 Loudness Dependence of Auditory Evoked Potentials (LDAEP)

There is an evidence that alterations of serotonin (5-HT) system functioning also play a crucial role in the pathophysiology of disabling negative symptoms. From post mortem and genetic studies on patients with negative symptoms a 5-HT dysfunction is documented. In addition, atypical neuroleptics and some antidepressants improve negative symptoms via serotonergic action. So far, no research has been done to directly clarify the association between the serotonergic functioning and the extent of negative symptoms. Wysse et al. (2013) based on the above, examined the status of brain 5-HT level in negative symptoms in schizophrenia by means of the loudness dependence of auditory evoked potentials (LDAEP). The LDAEP provides a well-established and noninvasive in vivo marker of the central 5-HT activity. They investigated 13 patients with schizophrenia with predominant negative symptoms treated with atypical neuroleptics and 13 healthy controls. The LDAEP of the N1/P2

component was evaluated by dipole source analysis and single electrode estimation at Cz. Psychopathological parameters, nicotine use, and medication were assessed to control for additional influencing factors. Schizophrenia patients showed significantly higher LDAEP in both hemispheres than controls. Furthermore, the LDAEP in the right hemisphere in patients was related to higher scores in scales assessing negative symptoms. A relationship with positive symptoms was not found. These data might suggest a diminished central serotonergic neurotransmission in patients with predominant negative symptoms.

It should be noted that only three papers specifically addressed ERPs in the deficit syndrome (Turetsky et al. 1998; Mucci et al. 2007; Li et al. 2013). Two studies provided data suggestive that the deficit syndrome is not simply a severe form of schizophrenia but more likely a separate clinical entity. Turetsky et al. (1998) while not employing the SDS, used the BPRS, SANS, and SAPS to address the criteria for the deficit syndrome. They examined the P300 component and found two patterns that cannot be seen as different grades of the same process. Patients with NDS showed the greatest reduction over the left temporal regions while the deficit subgroup showed the greatest reduction over the right parietal region. The second study specifically addressing DS, using the SDS, found a double dissociation where only NDS patients exhibited the asymmetrical left temporal P300 amplitude deficiency, while DS patients exhibited a decreased amplitude of the N100 (Mucci et al. 2007). Most recently, Li et al. (2013) compared a number of EPs between 21 patients with DS, 38 patients with NDS schizophrenia and 50 healthy control subjects. They included the P300 (both P3a and P3b), MMN, amplitudes and gating of the P50 MLAER, and the contingent negative variation (CNV). To our knowledge this is the only report examining the CNV in relationship to negative symptoms schizophrenia. The authors reported a great deal of similarity between the two schizophrenia groups. As compared to the healthy controls both patient groups exhibited delayed N1, N2, MMN, and P3a latencies as well as reduced N1, N2, and CNV amplitudes. Similarly, P50 gating was decreased in both groups. Only NDS, when compared to controls, showed delayed latency of P3b. Only DS patients showed delayed point A in CNV which correlated with poorer Global Assessment of Functioning scale but not with any individual negative symptom. These recent data suggest a significant overlap between the DS and NDS syndromes but with some distinctive characteristics that need further explorations in larger and perhaps unmedicated patients (Li et al. 2013).

4 Sleep Changes in Association with Negative Symptoms

Table 3 lists studies that directly reported on the association between sleep architectural changes and negative schizophrenia symptoms.

Decreased delta sleep in association with negative symptoms has been a relatively consistent finding in schizophrenia patients (Tandon et al. 2000). Of the

Table 3 Sleep

Study	Sample	Measurement	Assessment	Results
Ganguli et al. (1987)[a]	8 Sch (drug-naïve), 16 HC	Standard sleep analysis	BPRS, Wing negative symptoms scale	An inverse relationship between slow wave sleep and negative Sx
van Kammen et al. 1988[a]	10 Sch (unmedicat ed)	Standard sleep analysis	Scale for negative symptoms, Bunney-Hamburg global assessment scale for psychosis (83)	An inverse relationship between slow wave sleep and negative Sx
Tandon et al. 1989	10Sch and 10HC	Standard Sleep Analysis	BPRS, SANS, HAMD	Decreased SWS and Inverse correlation between SWS and severity of neg Sx
Tandon et al. (1992)	20 drug free and 20 drug-naive Sch and 15 HC	Standard sleep analysis	BPRS, SANS and 17-item HAMD	REM latency was inversely correlated with the severity of negative symptoms and unrelated to depressive symptoms. SWS did not differ between the groups and was unrelated to any clinical parameter
Neylan et al. (1992)[a]	18 Sch (haloperidol), repeat drug free (N = 9)	Standard sleep analysis	Bunny-Hamburg scale, SADS	An inverse relationship between slow wave sleep and negative Sx
Keshavan et al. 1995[a]	24Sch, Delusional disorder (N = 5), Un-medicated	Standard and automated sleep analysis	BPRS, SANS, SAPS, SCID	An inverse relationship between slow wave sleep and negative Sx
Kajimura et al. (1996)	Sch (N = 6) and 6 archival HC	Delta count during all night sleep	DSM-IV and BPRS	Decreased SWS and delta count particularly high amplitude significant negative correlation between the half-delta wave count and negative Sx
Kato et al. (1999)[c]	Sch (N = 7)	Standard sleep analysis	DSM-IV clinical	An inverse relationship between slow wave sleep and negative Sx
Tandon et al. (2000)[b]	Sch (drug free) (N = 60)	Standard sleep analysis	SADs and RDC	An inverse relationship between REM latency and slow wave sleep and negative symptoms
Müller et al. (2004)[b]	Sch (drug free, N = 10)	Standard sleep analysis	DSM-IV (clinical), PANSS	Decreased SWS and REM percentage

(continued)

Table 3 (continued)

Study	Sample	Measurement	Assessment	Results
Sekimoto et al. (2007)	11 Sch, 12 HC	Frontal delta wave count during sleep	BPRS	Delta count in frontal regions inversely correlated with BPRS negative symptoms scores
Poulin et al. (2008)[b]	Sch (first episode, drug naive) (N = 10), control (N = 30)	Spectral analysis	DSM-IV clinical and BPRS	Magnitude of absolute alpha correlated positively with negative symptoms and negatively with positive symptoms
Sekimoto et al. (2011)	17 Sch and 18 HC	Period-amplitude analysis of all night sleep	BPRS	Inverse correlation between neg Sx and delta wave counts in all brain regions
Yetkin et al. (2011)	13 Sch and 13 HC	Standard sleep analysis	BPRS, SANS, and SAPS	Sch had less total sleep time, less sleep efficiency, but no decrease in SWS. SWS was inversely correlated with formal thought disorder

[a] Possibly applicable
[b] *Likely applicable* description clear
[c] Description inadequate for a determination
BPRS Brief Psychiatric Rating Scale; *SADS* Schedule for Affective Disorders and Schizophrenia; *SANS* Scale for Negative Symptoms; *SAPS* Scale for Positive Symptoms; SCID Standardized Clinical Interview for DSM

13 studies identified, 10 reported decreased slow wave sleep (SWS) in association with negative symptoms. Of these 10 papers, seven found a significant negative correlation between the severity of negative symptoms and percent of SWS (i.e., with increased severity of negative symptoms, less SWS is noted).

Recent sleep studies depend heavily on computer-based analysis. Sekimoto et al. (2007) utilized a specialized program (the Medilog Sleep Analyzing Computer) to perform period-amplitude analysis of the delta wave count (delta half-wave analysis). They reported that schizophrenia patients in general exhibited a significant decrease in the percent of stage 2 sleep and a marked decrease of SWS. The delta half-wave count in the bilateral frontal regions was inversely correlated with BPRS negative symptoms scores. Poulin et al. (2008) reported a negative correlation between sleep absolute alpha activity and negative symptoms scores. Sarkar et al. (2010) reported a significant decrease in SWS, stages one and two as well as total sleep time in general but with no correlation with negative symptoms. On the other hand, Yetkin et al. (2011) found no evidence of a SWS abnormality in a group of 13 male schizophrenia patients (undifferentiated type).

Relatively more recently, Sekimoto et al. (2011) reported a significant inverse correlation between negative symptoms scores and delta wave counts in all regions examined (frontal, central, parietal, occipital). Utilizing self-report (Pittsburgh Sleep Quality Index), Lunsford-Avery et al. (2013) observed a strong association between negative symptoms severity (and not positive symptoms) and increased sleep dysfunction (no PSG data obtained).

5 Conclusions

Progress in the investigation of negative symptoms pathophysiology has been hindered by intrinsic heterogeneity of this symptom cluster. Primary and enduring negative symptoms are recognized as distinct disease processes with respect to broadly defined negative symptoms. Recent conceptualizations and factor analytic studies of both primary and broadly defined negative symptoms support two distinct domains: avolition and impaired emotional expression, probably related to separate pathophysiological mechanisms (Cohen et al. 2007). These sources of heterogeneity have seldom been considered in the electrophysiological literature. However, the field is rapidly changing and studies of the deficit syndrome as well as investigations of the separate domains of negative symptoms are rapidly increasing.

Two prominent/reasonably consistent electrophysiological correlates of negative symptoms emerge through this review: increased slow frequencies during wakefulness (as assessed by awake spectral EEG) and decreased slow wave sleep during night time recording.

While the largest group of studies identified were those related to EP/ERP findings, a consistent or strong trend was difficult to identify perhaps due to the tendency of different research groups to examine one particular EP component like

P300, MMN, or sensory gating. Studies examining a number of EP components simultaneously are sparse (Li et al. 2013). Despite the small number of studies and the varying EPs examined, the literature points to a deficit in the sensory gating of the mid-latency evoked responses reported from more than one laboratory (Boutros et al. 2009; Ringel et al. 2004; Louchart-de la Chapelle et al. 2005). Furthermore, a decreased amplitude of the N100 response has also been linked to the deficit syndrome (Mucci et al. 2007). It is of importance to note that a meta-analysis of the P300 ERP in schizophrenia found a correlation with positive but not negative symptoms (Jeon and Polich 2003). Mucci et al. (2007) were able to corroborate this finding in a group of well-characterized DS patients.

As is a direct reflection of the research expertise represented in a particular laboratory, most research groups tend to probe one physiological variable (e.g., ERP, EEG, or sleep). Multicomponent electrophysiological studies will help further define the abnormalities detected. For example, if an EEG or EP abnormality disappears during sleep this would influence the understanding of its pathophysiology as compared to the abnormality being persistent during sleep. If an EP abnormality is linked to a particular EEG state, this finding would be of significance for the identification of the neural circuitry mediating this abnormality.

The current level of knowledge is inadequate to propose a unifying theory of the pathophysiology underlying the described anomalies associated with the DS. However, most studies suggest pervasive bottom-up deficiencies that may lead to cascading information processing problems. This tentative conclusion is based on the observation that information processing abnormalities gleaned from EP studies (the only investigative methodology that can assess chronology at a millisecond by millisecond level in the intact behaving human), tend to occur earlier in the sequence of EPs and starting during periods that are commonly considered as "pre-attentive." Sleep deviations suggest a serious abnormality of the restorative deep sleep stages and the awake EEG abnormality suggest difficulty generating the faster frequencies, reflecting decreased ability to generate efficient smaller neuronal ensembles to deal with more focused or effective information processing.

A unifying hypothesis of the deviant oscillations during wakefulness (increased slow activity) and decreased slow wave sleep (SWS), could point to a dysfunction involving thalamocortical circuitry (Pinault 2011; Sekimoto et al. 2011). Thalamocortical circuits exhibit two fundamentally different modes of operation across the sleep-wake cycle: a state of tonic activation (desynchrony) during waking and REM sleep and a state of rhythmic synchronized activity during SWS (Steriade and Llinas 1988). Thalamic relay receives significant input from a number of brain stem structures and thus are subject to changes with a number of ascending neurotransmitter inputs. Furthermore, thalamic relay neurons also send collateral projections to the thalamic reticular nucleus which are reciprocally inhibitory (GABAergic) with thalamic nuclei (Siegel 2011). The thalamus (and more specifically the reticular nucleus) has been proposed to be important for the function of sensory gating which has been repeatedly shown to be deficient in schizophrenia and may be more specifically associated with negative symptoms (Krause et al. 2003). Kirkpatrick and Buchanan (1990) proposed a neural circuit that may be at

the heart of the DS. Components of this circuit include the amygdala, peri-amygdalar cortex, and parts of the prefrontal cortex. A number of thalamic nuclei (including the anterior, midline, mediodorsal, lateral anterior, and lateral dorsal as well as the intralaminar) have extensive connections with all these components (Clarke et al. 2010). The involvement of the thalamus is also supported by observation of worsening of somatosensory gating in patients with thalamic strokes with recovery of the function over time (Stain et al. 2002). Recent reviews suggest a central role for thalamic abnormalities in the generation of schizophrenia symptomatology (Byne and Hazlett 2009). Recent studies suggested an association between DS and genuine movement disorders (unrelated to antipsychotic treatment) pointing to cortico-striatal-thalamic circuits (Peralta et al. 2014). It could be hypothesized that abnormalities of the latter circuits might be related to avolition, while those concerning the limbic-thalamic circuits to the emotional expression domain of the negative symptoms.

Based on the above, it can be stated that while research on the electrophysiological correlates of the deficit syndrome and enduring negative symptoms remains minimal, available data strongly support the need and likely profitability of this line of investigation. Most notably is the absence of studies where EPs, EEGs and sleep studies are performed in the same individuals in order to examine the correlation and interrelationships among these deviations.

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References

Adler LE, Pachtman E, Franks RD, Pecevich M, Waldo MC, Freedman R (1982) Neurophysiological evidence for a defect in neuronal mechanisms Involved in sensory gating in schizophrenia. Biol Psychiatry 17:639–654

Adler LE, Waldo MC, Tatcher A, Cawthra E, Baker N, Freedman R (1990) Lack of relationship of auditory gating defects to negative symptoms in schizophrenia. Schizophr Res 3:131–138

Ahveninen J, Jääskeläinen IP, Osipova D, Huttunen MO, Ilmoniemi RJ, Kaprio J, Lönnqvist J, Manninen M, Pakarinen S, Therman S, Näätänen R, Cannon TD (2006) Inherited auditory-cortical dysfunction in twin pairs discordant for schizophrenia. Biol Psychiatry 60:612–620

Araki T, Niznikiewicz M, Kawashima T, Nestor PG, Shenton ME, McCarley RW (2013) Disruption of function-structure coupling in brain regions sub-serving self monitoring in schizophrenia. Schizophr Res 146:336–343

Arnfred S (2006) Exploration of auditory P50 gating in schizophrenia by way of difference wave. Behav Brain Funct 2:6

Baldeweg AK, Gruzelier JH, Hirrsch SR (2002) Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. Int J Psychophys 43:111–122

Barch DM, Dowd EC (2010) Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull 36:919–934

Blanchard JJ, Kring AM, Horan WP, Gur R (2011) Toward the next generation of negative symptom assessments: the collaboration to advance negative symptom assessment in schizophrenia. Schizophr Bull 37(2):291–299

Boutros NN, Zouridakis G. Overall J. (1991) Replication and extension of P50 findings in schizophrenia. Clinical EEG. 22(1):40-45

Boutros NN, Arfken C, Galderisi S, Warrick J, Pratt G, Iacono W (2008a) The status of EEG abnormality as a diagnostic test for schizophrenia. Schizophr Res 99:225–237

Boutros NN, Brockhaus-Dumke A, Gjini K, Vedeniapin A, Elfakhani M, Burroughs S, Keshavan M (2009) Sensory-gating deficit of the N100 mid-latency auditory evoked potential in medicated schizophrenia patients. Schizophr Res 113:339–346

Boutros NN, Gjini K, Arfken CL (2011) Advances in electrophysiology in the diagnosis of behavioral disorders. Expert Opin Med Diagn 5:441–452

Boutros NN, Korzyukov O, Jansen B (2004) Sensory-gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. Psychiatry Res 126:203–215

Boutros NN, Mears R, Pflieger PE (2008b) Sensory gating in the human hippocampal and rhinal regions: regional differences. Hippocampus 18:310–316

Boutros NN, Rustin T, Zouridakis G, Peabody CA, Warner MD (1993) The P50 auditory evoked responses and subtypes of schizophrenia. Psychiatry Res 47:243–254

Bowyer SM, Boutros N, Korzyukov O, Tepley N (2007) Supra-modal role for frontal cortex in sensory gating. Int Congr Ser 1600:367–370

Buchanan RW (2007) Persistent negative symptoms: an overview. Schizophr Bull 33:1013–1022

Buchanan RW, Javitt DC, Marder SR, Schooler NR, Gold JM, McMahon RP, Heresco-Levy U, Carpenter WT (2007) The cognitive and negative symptoms in schizophrenia trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. Am J Psychiatry 164:1593–1602

Byne W, Hazlett EA, Buchsbaum MS (2009) The thalamus and schizophrenia:current status of research. Acta Neuropathol 117:347–368

Chao LL, Knight RT (1995) Human prefrontal lesions increase distractability to irrelevant sensory inputs. NeuroReport 6:1605–1610

Clarke DL, Boutros NN, Mendez MF (2010) The brain and behavior: an introduction to behavioral neuroanatomy, 3rd edn. Cambridge, New York pp 156–166

Cohen AS, Saperstein AM, Gold JM, Kirkpatrick B, Carpenter WT Jr, Buchanan RW (2007) Neuropsychology of the deficit syndrome: new data and meta-analysis of findings to date. Schizophr Bul 33:1201–1212

Erwin RJ, Mawhinney-Hee M, Gur RC, Gur RE (1991) Midlatency auditory evoked responses in schizophrenia. Biol Psychiatry 30:430–442

Fehr T, Kissler J, Wienbruch C, Moratti S, Elbert T, Watzl H, Rockstroh B (2003) Source distribution of neuromagnetic slow-wave activity in schizophrenic patients–effects of activation. Schizophr Res 63:63–71

Foussias G, Remington G (2010) Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull 36:359–369

Freedman R, Waldo M, Bickford-Wimer P, Nagamoto H (1991) Elementary neuronal dysfunctions in schizophrenia. Schizophr Res 4:233–243

Galderisi S, Maj M (2009) Deficit schizophrenia: an overview of clinical, biological and treatment aspects. Eur Psychiatry 24:493–500

Ganguli R, Reynolds CF 3rd, Kupfer DJ (1987) Electroencephalographic sleep in young, never-medicated schizophrenics. A comparison with delusional and nondelusional depressives and with healthy controls. Arch Gen Psychiatry 44:36–44

Garcia-Rill E, Moran K, Garcia J, Findley WM, Walton K, Strotman B et al (2008) Magnetic sources of the M50 response are localized to frontal cortex. Clin Neurophysiol 119(2):388–398

Gjini K, Arfken C, Boutros NN (2010) Relationships between sensory "gating out" and sensory "gating in" of auditory evoked potentials in schizophrenia: a pilot study. Schizophr Res 121:139–145

Gm Winterer, Dorn K, Frick C (2000) Frontal dysfunction in schizophrenia: a newelectrophysiological classifier for research and clinical applications. Eur Arch Psychiatry Clin Neurosci 250:207–214

Gold JM (2008) Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull 34:835–847
Goldman-Rakic PS (1999) The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol Psychiatry 1(46):650–661
Green MF. (2006) Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry. 67 Suppl 9:3-8; discussion 36-42
Grunwald T, Boutros NN, Pezer N, von Oertzen T, Fernandez G, Schaller C, Elger CE (2003) Neural substrates of Sensory gating within the human brain. Biol Psychiatry 53:511–519
Guller Y, Ferrarelli F, Shackman AJ (2012) Probing thalamic integrity in schizophrenia using concurrent transcranial magnetic stimulation and functional magnetic resonance imaging. Arch Gen Psychiatry 69:662–671
Holroyd CB, Krigolson OE (2007) Reward prediction error signals associated with a modified time estimation task. Psychophysiology 44:913–917
Holroyd CB, Larsen JT, Cohen JD (2004) Context dependence of the event-related brain potential associated with reward and punishment. Psychophysiology 41:245–253
Horan WP, Foti D, Hajcak G, Wynn JK, Green MF (2012) Impaired neural response to internal but not external feedback in schizophrenia. Psychol Med 42:1637–1647
Huhn Z, Orbán G, Erdi P, Lengyel M (2005) Theta oscillation-coupled dendritic spiking integrates inputs on a long time scale. Hippocampus 15(7):950–962
Itoh T, Sumiyoshi T, Higuchi Y (2011) LORETA analysis of three-dimensional distribution of delta band activity in schizophrenia: relation to negative symptoms. Neurosci Res 70:442–448
Javitt DC, Doneshka P, Zylberman I, Ritter W, Vaughan HG Jr (1993) Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study. Biol Psychiatry 33:513–519
Jeon YW, Polich J (2003) Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology 40:684–701
Kajimura N, Kato M, Okuma T (1996) Relationship between delta activity during all-night sleep and negative symptoms in schizophrenia: a preliminary study. Biol Psychiatry 39:451–454
Kato M, Kajimura N, Okuma T, Sekimoto M, Watanabe T, Yamadera H, Takahashi K (1999) Association between delta waves during sleep and negative symptoms in schizophrenia. Pharmaco-eeg studies by using structurally different hypnotics. Neuropsychobiology 39:165–172
Keshavan MS, Cashmere JD, Miewald J, Yergani VK (2004) Decreased nonlinear complexity and chaos during sleep in first episode schizophrenia: a preliminary report. Schizophr Res 71:263–272
Keshavan MS, Miewald J, Haas G et al (1995) Slow-wave sleep and symptomatology in schizophrenia and related psychotic disorders. J Psychiatr Res 29:303–314
Kessler C, Kling A (1991) EEG power variation in schizophrenic subgroups: effects of emotionally salient stimuli. Biol Psychiatry 30:335–348
Kim DW, Kim HS, Lee SH (2013) Positive and negative symptom scores are correlated with activation in different brain regions during facial emotion perception in schizophrenia patients: a voxel-based sLORETA source activity study. Schizophr Res 151:165–174
Kirkpatrick B, Buchanan RW (1990) The neural basis of the deficit syndrome of schizophrenia. J Nerv Ment Dis 178:545–555
Kirkpatrick B, Buchanan RW, McKenney PD, Alphs LD, Carpenter WT Jr (1989) The Schedule for the deficit syndrome: an instrument for research in schizophrenia. Psychiatry Res 30:119–123
Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR (2006) The NIMH MATRICS consensus statement on negative symptoms. Schizophr Bull 32:214–219
Kirkpatrick B, Galderisi S (2008) Deficit schizophrenia: an update. World Psychiatry. 7:143–147
Knight RT, Grabowecky MF, Scabini D (1995) Role of human prefrontal cortex in attention control. In: Jasper HH, Riggio S, Goldman-Rakic PS (eds) Epilepsy and the functional anatomy of the frontal lobe. Raven Press, New York, pp 21–36

Knight RT, Scabini D, Woods DL (1989) Prefrontal cortex gating of auditory transmission in humans. Brain Res 504:338–342

Knott VJ (2000) Quantitative EEG methods and measures in human psychopharmacological research. Hum Psychopharmacol 15:479–498

Korzyukov OA, Pflieger ME, Wagner M, Bowyer SM, Rosburg T, Sundaresan K et al (2007) Generators of the intracranial P50 response in auditory sensory gating. NeuroImage 35(2):814–26

Kotini A, Anninos P (2002) Detection of non-linearity in schizophrenic patients using magnetoencephalography. Brain Topogr 15:107–113

Koukkou M, Lehmann D, Wackermann J, Dvorak I, Henggeler B (1993) Dimensional complexity of EEG brain mechanisms in untreated schizophrenia. Biol Psychiatry 33:397–407

Krause M, Hofffmann WE, Hajos M (2003) Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. Biol Psychiatry 53:244–253

Lengyel M, Huhn Z, Erdi P (2005) Computational theories on the function of theta oscillations. Biol Cybern 92(6):393–408

Leonard S, Mexal S, Freedman R (2007) Smoking, genetics and schizophrenia: evidence for self medication. J Dual Diagn 3(3–4):43–59

Li Z, Zheng B, Deng W (2013) Multi-components of evoked-brain potentials in deficit and nondeficit schizophrenia. Asia Pac Psychiatry 5:69–79

Louchart-de la Chapelle S, Levillain D (2005) P50 inhibitory gating deficit is correlated with the negative symptomatology of schizophrenia. Psychiatry Res 136:27–34

Lunsford-Avery JR, Orr JM, Gupta T (2013) Sleep dysfunction and thalamic abnormalities in adolescents at ultra high-risk for psychosis. Schizophr Res 151:148–153

Manchanda R, Norman R, Malla A (2008) EEG abnormalities and 3-year outcome in first episode psychosis. Acta Psychiatr Scand 117:277–282

Merrin EL, Floyd TC (1996) Negative symptoms and EEG alpha in schizophrenia: a replication. Schizophr Res 19:151–161

Mientus S, Gallinat J, Wuebben Y, Pascual-Marqui RD, Mulert C, Frick K, Dorn H, Herrmann WM, Winterer G (2002) Cortical hypoactivation during resting EEG in schizophrenics but not in depressives and schizotypal subjects as revealed by low resolution electromagnetic tomography (LORETA). Psychiatr Res 116:95–111

Mucci A, Galderisi S, Kirkpatrick B, Bucci P, Volpe U, Merlotti E, Centanaro F, Catapano F, Maj M (2007) Double dissociation of N1 and P3 abnormalities in deficit and nondeficit schizophrenia. Schizophr Res 92:252–261

Müller MJ, Rossbach W, Mann K (2004) Subchronic effects of olanzapine on sleep EEG in schizophrenic patients with predominantly negative symptoms. Pharmacopsychiatry 37: 157–162

Näätänen R, Gaillard AWK, Mäntysalo S (1978) Early selective-attention effect on evoked potential reinterpreted. Acta Psychol 42:313–329

Näätänen R, Kähkönen S (2009) Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. Int J Neuropsychopharmacol 12:125–135

Neylan TC, van Kammen DP, Kelley ME (1992) Sleep in schizophrenic patients on and off haloperidol therapy. Clinically stable versus relapsed patients. Arch Gen Psychiatry 49: 643–649

Nieuwenhuis S, Slagter HA, von Geusau A, Heslenfeld DJ, Holroyd CB (2005) Knowing good from bad: differential activation of human cortical areas by positive and negative outcomes. Eur J Neurosci 21:3161–3168

Noh K, Shin KS, Shin D (2013) Impaired coupling of local and global functional feedbacks underlies abnormal synchronization and negative symptoms of schizophrenia. BMC Syst Biol 10(7):30

Olincy A, Braff DL, Adler LE, Cadenhead KS, Calkins ME, Dobie DJ, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky

BI, Wagner BD, Freedman R (2010) Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the consortium on genetics of schizophrenia. Schizophr Res 119:175–182

Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, Koukkou M (1999) Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatr Res 90:169–179

Patterson JV, Hetrick WP, Boutros NN, Jin Y, Potkin S, Sandman C, Bunney WE (2008) P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. Psychiatry Res 158:226–247

Peralta V, Moreno-Izco L, Sanchez-Torres A, García de Jalón E, Campos MS, Cuesta MJ (2014) Characterization of the deficit syndrome in drug-naive schizophrenia patients: the role of spontaneous movement disorders and neurological soft signs. Schizophr Bull 40:214–24

Pfabigan DM, Alexopoulos J, Bauer H (2011) Manipulation of feedback expectancy and valence induces negative and positive reward prediction error signals manifest in event-related brain potentials. Psychophysiology 48:656–664

Pfefferbaum A, Ford MJ, White PM, Roth WT (1989) P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. Arch Gen Psychiatry 46:1035–1044

Pinault D (2011) Dysfunctional thalamic-related networks in schizophrenia. Schizophr Bull 37:238–243

Polich J (2007) Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118:2128–2148

Polich J, Kok A (1995) Cognitive and biological determinants of P300: an integrative review. Biol Psychol 41:103–146

Poulin J, Stip E, Godbout R (2008) REM sleep EEG spectral analysis in patients with first-episode schizophrenia. J Psychiatr Res 42:1086–1093

Ringel TM, Heidrich A, Jacob CP, Pfuhlmann B, Stoeber G, Fallgatter AJ (2004) Sensory gating deficit in a subtype of chronic schizophrenic patients. Psychiatry Res 125:237–245

Rockstroh B, Watzl H, Kowalik ZJ, Cohen R, Sterr A, Müller M, Elbert T (1997) Dynamical aspects of the EEG in different psychopathological states in an interview situation: a pilot study. Schizophr Res 28:77–85

Rosburg T, Boutros NN, Ford JM (2008) Reduced auditory evoked potential component N100 in schizophrenia: a critical review. Psychiatry Res 161:259–274

Sams M, Paavilainen P, Alho K (1985) Auditory frequency discrimination and event-related potentials. Electroencephalogr Clin Neurophysiol 62:437–448

Santos JL, Sánchez-Morla EM, Aparicio A, García-Jiménez MA, Villanueva C, Martínez-Vizcaíno V, Arango C (2010) P50 gating in deficit and non deficit schizophrenia. Schizophr Res 119:183–190

Sarkar S, Katshu MZ, Nizamie SH (2010) Slow wave sleep deficits as a trait marker in patients with schizophrenia. Schizophr Res 124:127–133

Schevernels H, Krebs RM, Santens P, Woldorff MG, Boehler CN (2014) Task preparation processes related to reward prediction precede those related to task-difficulty expectation. Neuroimage 84:639–647

Segalowitz SJ, Santesso DL, Chantziantoniou DK (2010) Retest reliability of medial frontal negativities during performance monitoring. Psychophysiology 47:260–270

Sekimoto M, Kato M, Watanabe T, Kajimura N, Takahashi K (2007) Reduced frontal asymmetry of delta waves during all-night sleep in schizophrenia. Schizophr Bull 33:1307–1311

Sekimoto M, Kato M, Watanabe T, Kajimura N, Takahashi K (2011) Cortical regional differences of delta waves during all-night sleep in schizophrenia. Schizophr Res 126:284–290

Siegel JM (2011) Sleep mechanisms and phylogeny. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 5th edn. Elsevier, St. Lious, MO, pp 76–91

Smucny J, Wylie K, Rojas D (2013) Evidence for gamma and beta sensory gating deficits as translational endophenotypes for schizophrenia. Psychiatry Res 214:169–174

Sponheim SR, Clementz BA, Iacono WG (2000) Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. Biol Psychiatry 48:1088–1097
Sponheim SR, Iacono WG, Clementz BA, Beiser M (1997) Season of birth and electroencephalogram power abnormalities in schizophrenia. Biol Psychiatry 41:1020–1027
Stains WR, Black SE, Graham SJ (2002) Somatosensory gating and recovery from stroke involving the thalamus. Stroke 33:2642–2651
Steriade M, Llinás RR (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68:649–742
Strauss GP, Waltz JA, Gold JM (2013) A review of reward processing and motivational impairment in schizophrenia. Schizophr Bull PMID: 24375459 [Epub ahead of print]
Strelets VB, Novototsky-Vlasov VY, Golikova JV (2002) Cortical connectivity in high frequency beta-rhythm in schizophrenics with positive and negative symptoms. Int J Psychophysiol 44:101–115
Tandon R, DeQuardo JR, Taylor SF (2000) Psychotic phasic and deficit enduring subtypes of negative symptoms: biological markers and relationship to outcome. Schizophr Res 45:191–201
Tandon R, Shipley JE, Eiser AS, Greden JF (1989) Association between abnormal REM sleep and negative symptoms in schizophrenia. Psychiatry Res 27:359–361
Tandon R, Shipley JE, Taylor S, Greden JF, Eiser A, DeQuardo J, Goodson J (1992) Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. Arch Gen Psychiatry 49:185–194
Thoma RJ, Hanlon FM, Moses SN, Ricker D, Huang M, Edgar C, Irwin J, Torres F, Weisend MP, Adler LE, Miller GA, Canive JM (2005) M50 sensory gating predicts negative symptoms in schizophrenia. Schizophr Res 73:311–318
Toyomaki A, Kusumi I, Matsuyama T (2008) Tone duration mismatch negativity deficits predict impairment of executive function in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 32:95–99
Turetsky B, Colbath EA, Gur RE (1998) P300 subcomponents abnormalities in schizophrenia I. Physiological evidence for gender and subtype specific regional pathology. Biol Psychiatry 43:84–96
van Boxtel GJM, Bocker KBE (2004) Cortical measures of anticipation. J Psychophysiol 18:61–75
van Kammen DP, van Kammen WB, Peters J, Goetz K, Neylan T (1988) Decreased slow-wave sleep and enlarged lateral ventricles in schizophrenia. Neuropsychopharmacology 1:265–271
Venables NC, Bernat EM, Sponheim SR (2009) Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia. Schizophr Bull 35:826–839
Walter WG, Cooper R, Aldridge VJ (1964) Contingent negative variation: an electric sign of sensori-motor association and expectancy in the human brain. Nature 203:380–384
Weiland BJ, Boutros NN, Moran JM, Tepley N, Bowyer SM (2008) Evidence for a frontal cortex role in mediating both auditory and somatosensory habituation: a MEG study. NeuroImage 42:827–835
Williamson PC, Kutcher SP, Cooper PW (1989) Psychological, topographic EEG, and CT scan correlates of frontal lobe function in schizophrenia. Psychiatry Res 29:137–149
Wolf DH, Turetsky BI, Loughead J, Elliott MA, Pratiwadi R, Gur RE et al (2008) Auditory Oddball fMRI in schizophrenia: association of negative symptoms with regional hypoactivation to novel distractors. Brain Imaging Behav 2(2):132–145
Wynn J, Horan P, Kring AM (2010) Impaired anticipatory event-related potentials in schizophrenia. Int J Psychophysiol 77:141–149
Wysse C, Hitz K, Hengartner MP, Theodoridou A, Obermann C, Uhl I, Roser P, Grünblatt E, Seifritz E, Juckel G, Kawohl W (2013) The loudness dependence of auditory evoked potentials (LDAEP) as an indicator of serotonergic dysfunction in patients with predominant schizophrenic negative symptoms. PLoS ONE 12(8):e68650. doi:10.1371/journal.pone.0068650
Yetkin S, Aydın H, Özgen F (2011) Sleep architecture in schizophrenia patients. Turk Psikiyatri Derg. Spring 22(1):1–9 (Article in Turkish)