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Electrophysiological Deficits in Schizophrenia: Models and Mechanisms

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1. Introduction

Schizophrenia a complex neuropsychiatric disorder, is characterized by core impairments including positive symptoms (hallucinations, delusions), negative symptoms (blunted affect, alogia, social deficits, anhedonia, avolition), as well as persistent neurocognitive deficits (memory, concentration, and learning). Positive symptoms usually show good response to currently approved medications, all of which act exclusively by blocking D2 receptors. Alternatively, the negative and neurocognitive symptoms respond poorly to D2 antagonists, and therefore persist even in treated patients. Developing new therapies to target treatment-resistant symptoms requires identification of neural endophenotypes associated with these deficits (Braff and Light, 2005). Additionally, neurophysiological biomarkers may be objective indices of prominent features in schizophrenia patients such as cognitive dysfunction (Javitt et al., 2008). The brain processes underlying neurocognitive symptoms can be investigated using various neurophysiological measures such as event related potentials (ERP) and electroencephalography (EEG). Event-related potentials and EEG oscillations represent coordinated neuronal activity and are thought to be a means to assess fundamental mechanisms of memory, attention, learning, and other cognitive functions. Consequently, these measures are likely to be an appropriate biomarker for brain abnormalities in schizophrenia. As such, great effort has been made to link particular electrophysiological features with relevant aspects of schizophrenia including psychopathology, clinical outcome, genetics, and pharmacology.

First, we will introduce the reader to the human EEG by giving an overview of the different components, highlighting each component's clinical relevance, as well as addressing its limitations. Subsequently, we highlight the characteristics of ERPs of schizophrenia. In the second part of the review, current preclinical models (i.e., transgenic, pharmacological, and environmental approaches) of EEG abnormalities in schizophrenia will be discussed. We then discuss potential requirements of future model and methods in order to provide further insight into the pathophysiological disease mechanism and thus allow the development and evaluation of new treatments.

2. Human electroencephalogram (EEG)

Electroencephalography was the first physiological technique used to examine the brain by recording electric field potentials with the capability to reflect both the normal and abnormal electrical activity of the brain. EEG evolved into an indispensable method for studying cerebral information processing, particularly due to the introduction of source localization techniques and the decomposition of event-related activity into its frequency components (Winterer, 2011). Conventionally, EEG is recorded from the scalp using numerous electrodes affixed to specific scalp locations and is represented as changes in potential difference. The scalp EEG reflects the summated potentials from a large synchronously activated population of pyramidal cells in the cerebral cortex. These potentials are thought to originate primarily from excitatory and inhibitory neural electric activity, including action potential (AP) and postsynaptic potentials (Dietrich and Kanso, 2010). A small subset of EEG applications (e.g. epilepsy and neurooncology) makes use of implanting the electrodes directly inside the brain. In this section, we will refer only to EEG measured from the scalp surface.

Recording paradigms. The pattern of the electrical brain activity is generally investigated in three different paradigms 1) at rest, 2) during sensory stimulation (tone, flash light), or 3) during a cognitively driven task. Oscillatory activity during the resting-state (baseline oscillations) is acquired while the subject lies still without engaging in a task. Irregularities in baseline oscillations are important indicators for non-physiological brain activity. Internal as well as external events (tone, flash light) induce changes in oscillatory activity, which are observable in the EEG. Commonly, the evoked EEG is assessed by engaging the patient in a research specific task (e.g. listening to tones, sort pictures, remember numbers). These complimentary techniques can be used to determine alterations in default as well as specific networks, and as such have been used to define measures of signal to noise processing in schizophrenia and related disorders.

Advantages and limitations. Compared to in vivo ligand binding and hemodynamic measures including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) respectively, the greatest advantage of the EEG is the high degree of temporal resolution, which is typically 1ms or less. Such rapid data acquisition allows one to record complex pattern of neural interactions occurring within a physiological time range. Alternatively, hemodynamic and ligand binding measures provide a higher degree of spatial resolution than is possible using EEG techniques. Currently, the signal source localization for EEG lacks millimeter scale resolution due to blurring through the skull and scalp. Additionally, inverse source localization techniques are not suitable for deep structures and reply heavily on the constraints and assumptions of the models used. Consequently many possible EEG generator configurations may explain any given pattern of scalp EEG. Therefore, good spatial and temporal resolution is typically obtained by combining EEG with fMRI imaging (Javitt et al., 2008).

2.1 Event-related Potentials (ERP)

Electroencephalography provides a method to investigate general function of the brain including its reaction to particular stimuli that will be represented as changes in the EEG, globally known as event-related potentials (ERP) or evoked potentials (EP). These event-related potentials are defined as the oscillatory brain responses that are triggered by the occurrence of particular stimuli (auditory, visual, somatosensory).

Auditory evoked potential. Significant voltage fluctuations are detectable resulting from evoked neural activity and allow one to measure distinct stages in neural information processing. Moreover, ERPs reflect sub-cortical and cortical information processing in real time and thus they provide a useful tool for examine cognitive mechanisms in both normal brain function and disorder-related impairments. Each acoustic stimulus consists of the three primary components frequency, intensity, and time (Weber et al., 1981). Frequency refers to the spectrum of sound in hertz (Hz) and relates to the location of physical stimulation along the basilar membrane of the cochlea and along the tonotopic representation of the central auditory pathways (G. Celesia, 2005). Relative to a control the intensity refers to a stimulus loudness which is expressed in decibels (dB). The third component time, commonly measured in either microseconds (μs) or milliseconds (ms), comprises duration, repetition rate, and phase of onset of the stimulus.

The flow of information through the brain is reflected by the sequence of ERPs peaks. Human auditory evoked potential consists of three subsets of latency-defined components corresponding to progression of brain activity related to the auditory stimulus through the auditory pathway: brainstem auditory-evoked potentials (BAEP), middle-latency auditory-evoked potentials (MLAEP), and long-latency auditory-evoked potentials (LLAEP). Early sensory responses characteristically occur within a 10-milisecond time period after the presentation of an auditory stimulus at high intensities (70-90 dB normal hearing level [nHL]). A cascaded activation of the brainstem nuclei along the auditory pathway generates six waves starting at the cochlear nuclear complex – in this regard, these responses are called brainstem evoked potentials (BAEP) or auditory brainstem potentials (ABP) and are represented by the roman numerals I-VI (Buchwald and Huang, 1975, Bolz and Giedke, 1982). The I to V interpeak latency represents the brainstem transmission time as well as the brainstem auditory process. BAEP have been shown to be effective in the evaluation of integrity of the peripheral and central auditory pathways (G. Celesia, 2005). Clinical applications of BAEP are suitable in hearing assessment, determination of hearing loss, evaluation of brainstem function, and diagnosis of neurological disorders. Although BAEP are widely applied in clinical practice, concerns about the quality, comparability, and reproducibility have been raised (Chiappa and Young, 1985). In fact, the BAEP varies considerably in relation to changing aforementioned auditory stimulus parameters. Standardization of recordings techniques with respect to variables such as the positioning of the electrodes, stimulus characteristics, and click presentation time is important to obtain reproducible BAEPs.

Middle-latency auditory evoked potentials (MLAEP), defined as responses between 10 and 50ms (including the peaks N0, P0, N20, P50), are thought to correspond to the stimulus transduction in the auditory thalamus and auditory cortex (Picton et al., 1974). Most likely, these responses are originated from the medial geniculate nucleus and the primary auditory cortex (Woods et al., 1987). Middle-latency potentials find clinical application in the assessment of hearing threshold and identification of auditory perception (G. Celesia, 2005). Additionally, MLAPs provide a reliable method to asses thresholds to low frequencies that are crucial for speech perception (G. Celesia, 2005). However, contrary findings have been reported regarding to the reliability of the MLAP which arises questions about their clinical use. For instance, there is no consensus in terms of the presence of MLAPs in children. Several studies report the MLAP to be reliably recordable (Mendel et al., 1977, Mendelson and Salamy, 1981), others found the MLAP to be absent or unstable (Skinner and Glattke, 1977, Davis et al., 1983). While present, MLAP may serve as an indicator of hearing

sensitivity, an absence of MLAP cannot be taken as an indication of hearing loss. Furthermore, in the normal population, the MLAP varies considerably, especially across age groups (Kraus et al., 1985). The difference in MLAP in normal subjects compared to MLAP in patients with neurological, cognitive, and speech disorders is also noted to be too small to equal an absent or abnormal MLAP with auditory pathway dysfunction. Longer latency components typically occur more than 50ms after acoustic stimulation reflecting the neural activity in the frontal cortex and cortical association areas (Gallinat et al., 2002). These potentials are predominately classified into obligate (N1, P1, P2) and task related components (P300, N400, MMN) referring to the dependence on characteristics of external (visual and acoustic) and internal stimuli, respectively. Thus, human LLAEP are mainly characterized by two major deflections, specifically the negative deflection N100, and the positive deflection P300 with latencies of 100 ms and 300 ms post, respectively. Abnormalities in LLAEP have been related with various type of psychopathology.

2.2 Components of the human ERP

The stages of information processing are mainly represented by following ERP components: P50, N100, P200, P300, and the mismatch negativity. P50 reflects the pre-attentive, N100 and P200 the early stages and P300 the late stage of information processing.

Sensory gating denotes the ability of the central nervous system (CNS) to inhibit or suppress the response to irrelevant or distracting sensory input in order to focus on task-relevant sensory information. Habituation following repeated exposure to the same sensory stimulus is an essential protective mechanism of the brain against flooding of the higher cortical centers with unnecessary information (Venables, 1964). A commonly used electrophysiological procedure to assess sensory gating in humans is the paired-click paradigm (PCP) (Adler et al., 1982, Boutros et al., 1993). During this task, a pair of identical brief auditory stimuli is presented at an interval of 500ms. Additionally, an interpair interval of 8-10s assure that the effects of one pair of stimuli do not carry over to the next pair (Zouridakis and Boutros, 1992). If inhibitory pathways are functioning normally, the amplitude of the response to the second stimulus (test response) is decreased because of inhibition pathways that are activated in response to a first (conditioning) stimulus. The quality of the sensory gating mechanism is expressed as the ratio of the two amplitudes (second amplitude/ first amplitude times 100)(Mazhari et al., 2011). Hence, low ratios indicate better sensory gating capability due to a stronger inhibition of irrelevant input.

Mainly, three evoked potential components are used to examine the sensory gating: P50, N100, and P200. Under physiological conditions the amplitudes of P50, N100, and P200 to the second stimulus (S2) in the pair are significantly reduced compared to the first stimulus (S1) reflecting an inhibitory mechanism to minimize the disruptive effects of the second repeating and therefore irrelevant stimulus (Williams et al., 2011). Peaking between 15 and 80 msec following stimulus presentation, P50 is the earliest major component that habituates to stimulus repetition. Attentional influences are minimal at this early stage of information processing making the P50 component optimal for the investigation of pre-attentive sensory mechanism (Grunwald et al., 2003). The N100, the largest component of the auditory evoked potential, has a peak latency of about 100ms and is a neurophysiological parameter reflecting arousal and attention (Strik et al., 1992). Its generation is conducted by a complex network of cortical areas (Rosburg et al., 2008). The amplitude of N100 is sensitive a long-list of individual related factors (e.g. attention, hearing threshold, motivation, drug and

smoking history) and physical characteristics of the stimulus (e.g., duration, intensity, rise time). N100 is primarily an exogenous component which is elicited by any discernible auditory stimulus, irrespective of attention. However, distinct differences between attended and unattended stimuli are observed (Rosburg et al., 2008). For example, the level of arousal has a modulating effect on the amplitude of the N100 evoked by unattended stimuli while the degree of selective attention influences the N100 amplitude evoked by attended stimulus. Auditory P200 is a positive event-related positive deflection automatically peaking roughly 200ms after stimulus presentation regardless of attention and task variables. However, its latency and amplitude co-vary with aspects of selective attention and stimulus encoding processes. P200 is reported to index early information processing, selective attention, and stimulus encoding (Shenton et al., 1989, Polich and Squire, 1993). Thus, the auditory temporal cortex has been highly implicated in P200 generation (Shenton et al., 1989). It is noteworthy that brain regions that are not primary sources of P200 may modify the response as a function of experimental conditions (e.g., attentive versus inattentive).

Mismatch Negativity. The ability to detect changes in auditory stimulus characteristics and adapt thereafter are basic neuronal functions that can be measured with ERPs in both, humans and animals. Mismatch negativity (MMN) reflects the context-dependent information processing which is required to compare a deviant incoming stimulus with the neural representation already stored in the transient auditory memory (Bomba and Pang, 2004). When a string of tones with a specific regularity (sequence of homogenous tones) is presented, the brain stores the features of this auditory stimulation in a short-duration neural memory trace (Ulanovsky et al., 2004). While this echoic memory is still active, each new auditory input is compared to the existing trace for a break of regularity (deviant tone), which generates a neuronal adaptation giving rise to the MMN (Naatanen, 2000). MMN is most frequently elicited in an auditory oddball paradigm. A sequence of repetitive standard stimuli is randomly interrupted by a deviant oddball stimulus which may differ in stimulus characteristics such as pitch, intensity, or duration. Generators are located in the auditory and frontal cortices (Giard et al., 1990, Alho, 1995). Of particular importance, MMN is evoked irrespective of attention (e.g. present in comatose patients) (Fischer et al., 2000). Peaking between 100 and 225ms, MMN is a difference wave between responses to frequent and deviant stimuli. In clinical neurosciences, MMN has been widely used in various applications, in particular in schizophrenia research, due to its good reproducibility and the ability to assess it without a task (Garrido et al., 2009).

P300. Probably the most extensive studied long-latency ERP component is the P300 (also termed P3), a time-locked positive deflection emerging 250 ms to 500 ms after attending stimulus. First described by Sutton et al. in 1965, P300 is thought to reflect an information processing cascade when attentional and memory mechanisms are engaged (Polich, 2007). Although related to the process of sensory stimulus mismatch detection, the P300 component represents an attention-driven memory comparison process in which every incoming stimulus will be revised to detect possible stimulus feature modifications. According to whether changes are present or absent, the electrophysiological recordings will differ. If no change can be detected, only sensory evoked potentials are recorded (N100, P200, N200). If a new stimulus is presented and the subject allocates attentional resources to the target, the neural stimulus representation is altered and the consequent update leads to the generation of P300 (Polich, 2007). Similar to the MMN, the auditory P300 is elicited in context of an oddball paradigm, but in contrast to MMN elicitation the generation of P300 requires the test-taking person to be attentive and respond physically or mentally to the

presented target. Commonly, subjects are instructed to either push a button following the infrequent target or to count deviants. The P300 is measured by quantifying its amplitude and its latency within a time window which varies (e.g. 250-500ms) as a function of the subjects age stimulus mode, and task conditions (Singh and Basu, 2009). P300 amplitude is also considered to index brain activity reflecting attention to incoming stimulus information when representations are updated (Polich, 2007, Turetsky et al., 2007b). The P300 latency is thought to be a measure of perceptual processing speed (Polich, 2007). The P300 consists of two subcomponents, an early potential P3a and a later component P3b. While P3a is evoked by any novel stimulus, the task-relevant P3b potential is only elicited during target stimulus processing (Javitt et al., 2008). P3a is hypothesized to be generated by stimuli which change the content of the working memory. This attentional-driven neural activity may then be transmitted to brain areas associated with memory storage and subsequently generate the P3b. Supportively, time frequency analyses indicate that theta and alpha activity govern the relationship of the P3a to attention and P3b to memory processing (Intriligator and Polich, 1994, Spencer and Polich, 1999, Polich, 2007). The P3a appears to be sensitive to specific neurotransmitters; in particular dopamine and glutamate have been implicated in the mediation of P3a. Specifically, clinical populations associated with reduced dopamine levels (e.g., Parkinson's disease, rest-less leg syndrome) exhibited deficient P3a (Hansch et al., 1982, Stanzione et al., 1991). Conversely, pharmacological enhancement of dopamine level was shown to increase P3a in patients with low baseline amplitudes (Takeshita and Ogura, 1994). In addition, glutamatergic and GABAergic disequilibrium impair the generation of P3a. Watson found both the NMDA receptor antagonist ketamine and the GABA-A receptor agonist thiopental to reduce P3a amplitude, while ketamine also shortened the P3a latency (Watson et al., 2009). The second P300 subcomponent, P3b, is thought to serve as a measure of evaluation of environmental signals including contextual information (Squires et al., 1976, Barcelo and Knight, 2007). Furthermore, perceptual analysis and response initiation are suggested to be reflected by P3b. The locus coeruleus–norephedrine system (LC-NE) is of importance for the regulation of sensory signal transmission and was suggested to underlie the generation of P3b (Nieuwenhuis et al., 2005). Pharmacological evidence emerges from studies in which subjects were exposed to nicotine, a NE-release mediating agent, inducing a significant increase in P3b amplitude (Polich and Criado, 2006).

In summary, P300 and its subcomponents may provide an insight to the mechanisms and pathways of various cognitive processes. However, the understanding and investigation of these coponents is coined by some noteworthy limitations. Studies of the differences in the P300 observed across various patient populations have been highly variable (Polich, 2007). Specifically, in only 10-15% of normal young adults the P3a can readily be observed. Despite simplicity of the task situation and the reliability of observing ERPs in the oddball paradigm, the cerebral mechanisms producing the P300 remain elusive. As such, the neural generators of P300 are imprecisely delineated (Soltani and Knight, 2000, Eichele et al., 2005, Linden, 2005).

2.3 ERP measurements and analysis

The primary step of all ERP analysis is to extract the event-related portion of the recorded field potentials. Detecting ERP activity within ongoing activity is a general problem since brain responses to individual sensory, cognitive, or motor events are relatively small compared to the steadily ongoing background activity, also called noise, (i.e., the activity not

related to the stimulus). Thus, to enhance the responses in contrast to the background noise (i.e., improve signal-to-noise ratio) the analysis of ERP is done by averaging the oscillatory activity of a series of trials.

Power measure. Power reflects the amplitude of an oscillation. Amplitude (μV) is defined as difference between the mean pre-stimulus baseline voltage and the largest positive or negative going peak of the ERP waveform with in a time window. Its latency (ms) defines the time from stimulus onset to the point of maximum amplitude (Polich, 2007). For a stationary signal, in which the EEG does not change over time, the Fast-Fourier Transform (FFT) is used to spectrally decompose the time-invariant signal into component frequencies. The power spectrum yielded by FFT analysis is used for resting-state tasks. The analysis of non-stationary neural activity requires signal-processing methods that compute changes in oscillatory activity at a particular frequency across time. Oscillatory responses can be categorized by their phase- and temporal-relationship to repeated trials of a sensory or cognitive event (Galambos and Makeig, 1992, Tallon-Baudry et al., 1998). Oscillations directly in phase with a stimulus (i.e., phase- and time-locked) are called evoked oscillations. Induced oscillatory activity is modulated by a stimulus but is not strictly phase-locked to event onset (i.e., time- but not phase-locked). Oscillatory activity that is in-phase with a stimulus averages across trials to produce an evoked-response assuming that (1) the delay of the electrical brain responses relative to the stimulus is invariable across the testing trial; and (2) the ongoing background activity is steady (Da Silva, 2005). In the time domain, induced oscillations tend to average out and thus require different single-trial signal processing methods for identification. Finally, total power refers to the sum of evoked and induced power and is typically represented as difference from or a percentage change from pre-stimulus baseline power at each frequency (Gandal et al., 2010).

Phase measures. The main approach is to decompose a neural time series into phase information at a given frequency. Applying time-frequency transforms, one can investigate changes in frequency-specific measures during a given task with millisecond precision. **Event-related spectral perturbation (ERSP)** is a measure of change of power from baseline associated with a stimulus presentation, and includes both phase locked and non-phase locked activity (Shin et al., 2010). Time-frequency transforms also provide measures of the phase of oscillations, allowing for investigation of phase-synchrony. **Phase-synchrony** is independent of oscillatory amplitude and is therefore thought to be a more direct measure of the synchronization of neural signals. The phase locking factor (PLF) (i.e., intertrial coherence, ITC) describes the similarity in phase at a given point in time across trials at a single electrode site. This measure is unitless, ranging from 0 to 1.

Auditory Steady State Responses (ASSR) are middle-latency auditory evoked potentials triggered by presentation of auditory stimuli at rates between 1 and 200 Hz or by continuous tones modulated in amplitude and or frequency. The responses from both types of stimuli are a metric for looking at synchronous neuronal activity in the brain's auditory processing. Conventionally, values of 0.5, 1, 2 and 4 kHz are used for the continuous carrier tone whereas repetitive stimulus trains are often presented around 40 Hz (Galambos et al., 1981, Herdman and Stapells, 2001, Luts and Wouters, 2005). The modulation of the carrier tone occurs in amplitude or frequency at a set rate. The response to these periodic modulations or stimulation trains is measured for phased locking and amplitude. ASSR stimuli contrast with the broadband clicks delivered with Auditory Brain Responses (ABRs). Whereas the auditory stimulus of the ABRs consist of a spectrum of tones in one stimulus

click, the ASSR stimulations (especially with continuous tone amplitude modulation) can target specific tones, giving ASSRs a level of frequency-specific information sensitivity that is not present in the ABR metric (Roeser, 2007). ASSRs therefore give a consistent measurement of brain responses reflective of information processing and hearing thresholds without the need of subject involvement.

Frequencies. Oscillatory activity is generally evaluated within EEG frequency ranges: delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (>30 Hz). Furthermore, each range is linked to specific perceptual and cognitive processes as well as behavioral states (Table 1) (Basar et al., 2001). In 1929, Hans Berger first depicted measurable brain activity at a frequency of ~10Hz and termed this oscillation **alpha** (Berger, 1929). Alpha oscillations are correlated to brain function such as inhibition, attention, consciousness and primarily generated in thalamus, hippocampus, and cortical regions (Uhlhaas and Singer, 2010). The **theta** range is associated with perceptual processing, learning, memory, and synaptic plasticity (Huerta and Lisman, 1993). Cortico-hippocampal circuits have been found as key generators of the rhythm (Ehrlichman et al., 2009a). **Beta** oscillations are believed to be generated in overall cortical structures and are involved in sensory gating, attention, and long-term synchronization (Kopell et al., 2000, Gross et al., 2004, Hong et al., 2008a). **Gamma** oscillations have received special attention in the research of neuropsychiatric disorders due to their alleged role in sensory binding, selective attention, associative and perceptual learning, encoding and retrieval of memory traces (Singer, 1993, Bragin et al., 1995, Chrobak and Buzsaki, 1998, Miltner et al., 1999, Fries et al., 2001). Gamma-band oscillations depend on intact function of the fast-spiking GABAergic (parvalbumin containing) interneurons (Fuchs et al., 2001). These subsets of inhibitory GABAergic interneurons, located in hippocampal and cortical areas, are proposed to play a primary role in the generation of the gamma oscillations (Uhlhaas and Singer, 2010).

Frequency range	Primary generators	Function
Alpha (8-12 Hz)	Thalamus, hippocampus, cortical regions	Inhibition, attention, consciousness
Theta (4-7 Hz)	Cortico-hippocampal circuits	Perceptual processing, learning, memory, synaptic plasticity
Beta (13-10 Hz)	Overall cortical structures	sensory gating, attention, and long-term synchronization
Gamma (30-200 Hz)	Hippocampal and cortical	Perception, selective attention, consciousness, encoding and retrieval of memory traces

Table 1. Functional correlates of neural oscillations

3. EEG abnormalities in schizophrenia

3.1 Abnormalities in obligate ERP

Neurophysiological measures have been widely applied with regard to schizophrenia since they provide the ability to index abnormalities in information processing, to localize

involved brain regions and correlate well with negative and cognitive deficits. Supporting evidence from EEG studies suggest that the core pathophysiology of schizophrenia is related to abnormal brain dynamics, neural synchronization, and connectivity. Schizophrenia patients exhibit deficits in amplitude and/or gating of the P50, N100, and P200 obligate components, as well as reductions in task related mismatch negativity, P3a, and P3b. Thus, this section will introduce readers to the characteristic ERPs of schizophrenia, which are typified by alterations in all amplitude, latency, and gating of several key components relative to healthy population.

Mismatch negativity provides a useful tool for investigating mechanism underlying cognitive dysfunction in patients suffering from schizophrenia as well as autism, dyslexia, and dementia. Initially, Shelley and colleagues found abnormalities of MMN in individuals with schizophrenia (Shelley et al., 1991). Similarly, more than 30 studies report a significant attenuated MMN amplitude in patients with schizophrenia, for both frequency and latency (Umbricht and Krljes, 2005). Thus, these findings are believed to reflect the degraded auditory perception, a feature linked with schizophrenia (Naatanen, 2003). For instance according to Javitt, schizophrenia subjects exhibit impairments not only in generation of frequency-MMN, but also in tone-matching performance (Javitt, 2000). Additionally, studies have noted a correlation between the magnitude of the MMN and disease severity (Catts et al., 1995). However, it is necessary to note that changes of MMN parameters (e.g., prolongation of latency and reduction of amplitude) are not sufficiently specific to diagnose particular disease. Disturbances in the glutamatergic system, more specifically the inadequate NMDA-receptor neurotransmission, have been implicated in neurocognitive deficits of schizophrenia (Javitt and Zukin, 1991). Thus, the assumption that MMN depends on intact NMDA receptor signaling makes MMN a particularly interesting paradigm for schizophrenia research. NDMAR antagonists, such as ketamine and phencyclidine (PCP), have been shown to selectively abolish the MMN suggesting the NMDAR-dependent neurotransmission to underlie deficits in MMN generation and echoic memory (Javitt, 2000, Umbricht et al., 2000, Naatanen, 2003). Furthermore, MMN has been proved useful in clinical investigations of schizophrenia patients due to its robustness to changes in attention and performance (Garrido et al., 2009). Intrestingly, also siblings of schizophrenia patients have been reported to exhibit impaired working memory reflected in a reduction of the MMN amplitude (Sevik et al., 2011). Although the literature contains conflicting results, MMN may serve as an index of genetic predisposition to schizophrenia and disease progression (Jessen et al., 2001, Michie et al., 2002, Shinozaki et al., 2002).

Disturbances in information processing are key features of schizophrenia (Braff, 1993). Insufficient inhibitory processing of repetitive, irrelevant acoustic stimuli has been reported in patients as well as their first-degree relatives (Bramon et al., 2004, de Wilde et al., 2007). Using a double-click auditory paradigm, Adler and others have noted that schizophrenia patients have a diminished **gating** of the auditory P50 (Adler et al., 1982) (Judd et al., 1992, Olincy and Martin, 2005). While in healthy subjects a repeated presentation of an auditory stimulus causes a >60% reduction in S2 amplitude, schizophrenia patients routinely fail to suppress their response to the second click (Adler et al., 1982, Braff and Geyer, 1990, Stevens et al., 1991). Adler and colleagues also noted a diminishment of the amplitude and latency of the response to the first stimuli in unmedicated individuals with schizophrenia (Adler et al., 1986). Neuroleptics increase **P50** latency and amplitude, but do not normalize conditioning-testing ratios. As such, the observed gating deficits may actually result as an

epiphenomenon of medication, rather than as part of the disease (Siegel et al., 2005). Despite this limitation, P50 gating has been interpreted by some to demonstrate reduced capability to extract relevant from irrelevant information, leading to an overload of information reaching consciousness and cognitive fragmentation (Venables, 1960, Patterson et al., 2008). This may contribute to many of the difficulties people suffering from struggle with including the inability to stay focused during conversation or the being overwhelmed by the physical environment (Freedman et al., 1996, Turetsky et al., 2007b, Williams et al., 2011). The brain regions and their neural dynamics that underlie the malfunctioning of inhibitory processes still remain to be determined. Furthermore, it should be noted that this P50 gating phenomenon has not been replicated outside a small number of institutions, suggesting a large impact of operator processing on the measure (de Wilde et al., 2007). As such, P50 gating is not an ideal measure of signal processing and should not be used in place of more robust and reproducible findings using other ERP measures and components.

Patients with schizophrenia exhibit deficits in **N100** generation, especially at long interstimulus intervals (ISI) and extremely short ISIs. Amplitude reduction and latency delay of the auditory N100 are robust physiological abnormalities in schizophrenia (Roth et al., 1981, Laurent et al., 1999). However, the findings are inconsistent and seem to depend on the experimental conditions used (Davis et al., 1966, Pritchard, 1986). Reduced N100 amplitude reflects deficits in mechanism involved in initial sensory processing and early selective attention, prominent features seen in schizophrenia (Strik et al., 1992, Frangou et al., 1997). Although N100 amplitude reduction is relatively independent of symptom severity, Ahveninen and colleagues proposed N100 reduction could serve as an endophenotypic trait marker of functional brain changes related to genetic predisposition to schizophrenia (Ahveninen et al., 2006). There is some evidence that N100 amplitude reduction is also seen in first-degree relatives (Blackwood et al., 1991, Turetsky et al., 2008). For instance, a combined EEG/MEG study on monozygotic and dizygotic twins discordant for schizophrenia revealed an N100 amplitude reduction in both schizophrenia patients and their unaffected siblings (Ahveninen et al., 2006). More evidence for the heritability of the N100 amplitude comes from similar twin studies (Blackwood et al., 1991, Frangou et al., 1997). Furthermore, a reduction in N100 amplitude appears not to be specific to schizophrenia in that it is also reported in patients with bipolar disorder, and hypothyroidism (Umbricht et al., 2003, Oerbeck et al., 2007). Reduced gating of the N100 response to repeated stimulation has also been demonstrated in schizophrenia (Turetsky et al., 2008).

The auditory **P200** indexes early stimulus processing and thus is informative to study in schizophrenia, which has been linked to deficits in early information processing. Numerous reports have demonstrated that amplitude and gating of the P200 are reduced in schizophrenia (Roth et al., 1981, Boutros et al., 2004a, Boutros et al., 2004b, Lijffijt et al., 2009a, Gjini et al., 2010). Moreover, reduced amplitude appears to be related to negative symptoms, in particular anhedonia and avolition (Shenton et al., 1989). P200 gating shows a positive relationship to attentional performance and the post-attentive cognitive P300 response (Boutros et al., 2004b, Lijffijt et al., 2009b). Pharmacological studies indicate various neurotransmitters, such as glutamate and dopamine, contribute to the generation of P200. As such, healthy people display schizophrenia-like decreases in P200 amplitude during acute exposure to ketamine (Murck et al., 2006). Moreover, amphetamine administration reduces P200 amplitude to the first stimulus in an auditory gating paradigm, suggesting

that decreased NMDA-mediated transmission may produce the observed attenuation of the P200 through facilitation of dopamine release (Connolly et al., 2004). Various family studies indicate that there are abnormalities in P200 among relatives of schizophrenia patients, suggesting a substantial genetic component to this endophenotype (Frangou et al., 1997, Freedman et al., 1997). Similar to N100, the P200 has further been suggested as a measure for sensory gating since both components produce less inter-subject and inter-protocol variability as compared to P50.

In the oddball paradigm, the **P300** response indexes cortical responses related to recognizing and assessing the significance of rare stimuli. Meta-analysis has shown that schizophrenia patients have significantly reduced P300 amplitudes and that their P300 latency is significantly delayed compared to normal controls (Bramon et al., 2004). Diminished P300 may indicate the presence of unsteady background activity that interferes with detecting the identity and salience of the task-related stimulus (Pfefferbaum et al., 1989). Additionally, Pritchard suggested that P3 amplitude attenuation may potentially serve as a trait marker for the negative symptoms of schizophrenia (Pritchard, 1986). Several studies support a negative correlation between P3 amplitude and severity of negative symptoms, but emphasize its validity only in medicated patients (Roth et al., 1975, Pfefferbaum et al., 1989). Anti-psychotic medications were also shown to significantly affect the amplitude but not latency of P300 (Bramon et al., 2004). Interestingly, it has been proposed that the P300 waveform is a physiological correlate of an update in working memory related to changes in the environment (Donchin and Isreal, 1980). This idea is supported by the finding that P300 amplitude and latency correlate with neuropsychological performance scores in patients. Notably, there are correlations between decreased P300 amplitude, lower IQ and poorer memory performance as well as increased P300 latency and lower IQ, poorer total memory scores, and serial clustering (Shajahan et al., 1997). Evidence that P300 abnormalities may serve as an indicator for genetic vulnerability arises from recent studies which found similar P300 alteration in first-degree relatives including decreased amplitude and increased latency (Saitoh et al., 1984, Blackwood et al., 1991, Kidogami et al., 1991).

In addition to the task related P3, also known as the P3b, an automatic, task-independent portion of the P3 called the P3a is thought to be modulated by both glutamate and dopamine (Siegel et al., 2003). A growing body of evidence suggests that there is also a reduction in P3a amplitude in schizophrenia (Mathalon et al., , Mathalon et al., 2000, Alain et al., 2002, Devrim-Ucok et al., 2006, Ford et al., 2008, van der Stelt and van Boxtel, 2008, Mathalon et al., 2010). Prolongation of P3a latency is also observed in patients (Frodl et al., 2001). Within the schizophrenia population, patients with prominent auditory hallucinations manifest a P3a amplitude reduction compared to those without hallucinations (Fisher et al., 2010). This data has been interpreted to indicate that hallucinations reflect a preferential attention to internally generated brain activity, relative to incoming exogenous stimuli (Fisher et al., 2008). Furthermore, P3a has been linked to functional outcomes in schizophrenia in that reduced P3a amplitude is associated with extended illness duration and increased depression-anxiety symptoms (Mathalon et al., 2000, van der Stelt and van Boxtel, 2008).

Deficient processing of contextual information is a prominent feature of cognitive dysfunction in schizophrenia. Thus, P3b response has been extensively studied in schizophrenia and shows promise both as a measure of attentional processes during signal detection and as a predictor of performance on formal laboratory tests of cognition.

Suppressed P3b amplitude is a widely replicated finding in schizophrenia, while P3b latency elongation is less consistently reported (Blackwood et al., 1991, Ford et al., 1992, Roxborough et al., 1993, Coburn et al., 1998, Jeon and Polich, 2003). Most investigations of P3b have been conducted in chronic schizophrenia populations. Thus, it is of considerable interest to determine if these abnormalities are present at onset or are exacerbated by chronicity. To address this question, few studies have investigated the P3b component in first-episode schizophrenia (FES) and consistently report a reduction in P3b amplitude as well as prolonged latencies (Hirayasu et al., 1998, Brown et al., 2002, Demiralp et al., 2002, Wang et al., 2003). Furthermore, the P3b amplitude appears to correlate inversely with the disorder's duration (Olichney et al., 1998, Mathalon et al., 2000, Martin-Loeches et al., 2001). Brown and others identified similarities in P3b amplitudes in FES and CS patients (Hirayasu et al., 1998, Brown et al., 2002). Similarly, unaffected first-degree relatives of patients have frequently been reported to exhibit reduced P3b amplitudes (Blackwood et al., 1991, Kidogami et al., 1991, Roxborough et al., 1993). Additionally, most studies of P3 and its subcomponents have been performed in medicated patients. Thus, the effect of neuroleptics on these ERP components remains controversial. Some studies suggested that antipsychotic medication increases the P3b amplitude, in contrast to others which failed to replicate this finding (Pfefferbaum et al., 1989, Ford et al., 1994, Coburn et al., 1998, Umbricht et al., 1998). Lastly, it is important to note that the alterations of P3a and P3b are not specific to schizophrenia. For instance, bipolar depression is linked to similar impairments. Although the lack of specificity is a limitation with respect to addressing the unique pathophysiology of schizophrenia, the P3 family may still serve as a trait marker for schizophrenia vulnerability.

3.2 Event-related Spectral Perturbations (ERSP) abnormalities in schizophrenia

Neural oscillation and their synchronization are thought to reflect important mechanisms for interneural communication and binding of information that is processed in distinct brain areas (Roach and Mathalon, 2008). These oscillations are decomposed in order to examine individual frequency ranges. These frequency domains are linked to distinct cognitive and perceptual processes, some of which are known to be impaired in schizophrenia. Therefore, this section will discuss the schizophrenia-like alterations in time-frequency measures in baseline, evoked and non-evoked auditory responses across all frequency. Furthermore, a growing body of evidence indicates that people with schizophrenia also display abnormal EEG rhythms, in both high (beta and gamma) and low frequency bands (delta and theta). Contemporary EEG studies mainly focus on gamma oscillations because this range is thought to reflect a fundamental mechanism to integrate neural networks and play a critical role in cognitive function (Tiitinen et al., 1993, Gandal et al., 2010). Alternatively, earlier EEG studies in schizophrenia focused primarily on lower frequencies and found substantial evidence of abnormalities.

Increased pre-stimulus **theta-** and **delta**-band activity have consistently been observed in schizophrenia, occurring; 1) both locally and among distant electrodes; 2) regardless of medication history, and 3) in both first-episode and chronic patients (Morihisa et al., 1983, Morstyn et al., 1983, Sponheim et al., 1994). Converging evidence from magnetic resonance imaging studies supports that the default network in schizophrenia tends to be overactive (Fehr et al., 2003, Harrison et al., 2007). Positive symptoms were found to positively correlate with an elevated resting-state theta activity in certain brain areas (Garrity et al.,

2007). Contrary to resting-state activity, a number of studies using time-frequency measures revealed a reduction in theta and delta power of both phase locked and non-phase locked responses to an auditory stimulus in individuals with schizophrenia (Ford et al., 2008, Doege et al., 2009). Although a number of abnormal findings have been reported in the delta frequency range among people with schizophrenia, these data have been inconsistent across studies (Siekmeier and Stufflebeam, 2010).

Several investigators reported reduced or even absent power and coherence of **alpha** activity in schizophrenia during resting EEG and sustained attention (Itil, 1979, Merrin and Floyd, 1992). Also, Sponheim and others noted that individuals with schizophrenia exhibit reduced alpha activity, along with increased neighboring frequencies in the theta and beta bands. However, within the patient group no further differences were found between first-episode and chronic patients or between medication-naïve and medicated patients (Sponheim et al., 1994, Boutros et al., 2008). This consistency among clinical populations suggests that these abnormalities are a stable characteristic of schizophrenia and not treatment-related or duration-dependent. These EEG alpha alterations appear to correlate with the severity of negative symptoms. Indeed, repetitive transcranial magnetic stimulation was reported to improve negative symptoms and concomitantly to increase the alpha activity amplitude (Jin et al., 2006). As reviewed above, alpha oscillatory activity is associated with attention, which is impaired in schizophrenia. Investigation of evoked and induced alpha oscillations in schizophrenia revealed reduced alpha power and impaired ability to synchronize the phase of ongoing alpha activity. Greater trial-by-trial variability may be due the interference of ongoing background brain activity with the recruitment of neural systems which is indispensable for the processing of sensory information. For example, disturbed phase-locking leads to an increased trial-by-trial variability and diminished amplitude of certain ERP components, such as the N100 (Makeig et al., 2000, Gallinat et al., 2004, Haenschel et al., 2009, White et al., 2009). The influence of alpha oscillations on N100 is mirrored by a positive correlation between attention and N100 amplitude. Taken together, this may delineate the mechanism of impaired attention in schizophrenia. Furthermore, White proposed that an interaction between alpha and **gamma** oscillations is necessary for high fidelity and integrated communication within and across brain structures, facilitating coherent sensory registration (White et al., 2009). Given that a growing body of evidence also reveals disturbances in gamma oscillations in schizophrenia, it is possible that the interaction between early gamma and evoked alpha activity is diminished in schizophrenia. Gamma abnormalities have been reported in a variety of contexts, including in sensory-driven, cognitive, and resting-state paradigms. These deficits are present at first-episode psychosis, in unmedicated patients, and, to a lesser degree, in unaffected relatives, suggesting that abnormal gamma synchrony is a heritable feature of schizophrenia(Rodin et al., 1968b, Leicht et al., 2009)Symond et al., 2005). In resting-state paradigms, several studies reported elevated high-frequency EEG activity in schizophrenia (Finley, 1944, Itil et al., 1972, Fenton et al., 1980). Accordingly, two large studies found elevated pre-stimulus gamma power in schizophrenia patients during auditory paradigms (Winterer et al., 2004, Hong et al., 2008b). However, no group-differences in pre-stimulus gamma power were observed in smaller study, perhaps reflecting a need for larger sample sizes to detect subtle changes (Brockhaus-Dumke et al., 2008). Numerous studies have also investigated evoked and induced gamma oscillatory activity in schizophrenia. The overall findings suggest a reduction in stimulus-related gamma-band oscillations (Leicht et al., ,

Basar-Eroglu et al., 2009, Leicht et al., 2010a, Leicht et al., 2010b) (for review see (Gandal et al., 2010). However, not all studies found differences in evoked gamma-activity between patients and healthy comparison individuals, again suggesting that gamma band abnormalities may be subtle and require relatively large samples with sufficient power to detect population differences (Blumenfeld and Clementz, 2001, Brockhaus-Dumke et al., 2008).

Finally, lower levels of **beta** oscillatory activity have been observed in patients with schizophrenia (Rutter et al., 2009). In sleep studies, unmedicated patients had higher beta power at all stages of the sleep compared to healthy individuals (Tekell et al., 2005). Alternatively, deficient power and synchronization of evoked and induced EEG rhythms in the beta and gamma bands have frequently been reported (Clementz et al., 1997, Cho et al., 2006, Uhlhaas et al., 2006). Interestingly, these findings were replicated in medication-naïve and chronically medicated patients. However like other frequencies, contradictory and negative finding exists. Thus, few studies report an augmentation in evoked beta activity, which may be due to methodological or analytical differences (for review see (Uhlhaas and Singer, 2010).

3.3 Auditory steady-state response abnormalities in schizophrenia

Auditory steady-state auditory responses (ASSRs), in which the evoked potential entrains to stimulus frequency and phase, are reduced in amplitude and phase locking in patients with schizophrenia, particularly at 40 Hz (Kwon et al., 1999, Brenner et al., 2003, Light et al., 2006, Krishnan et al., 2009). Importantly, these deficits are present in schizophrenia patients during their first hospitalization. Several animal models of schizophrenia display similar ASSR disruption as those found in humans (Spencer et al., 2008, Vohs et al., 2010). These issues suggest deficiencies in the coordinated timing of neural populations within specific types of networks (Maharajh et al., 2010). The Gamma frequency has been correlated with many of the neuro-cognitive behaviors that are disrupted in schizophrenia (Haig et al., 2000). Thus, ASSR in the gamma spectrum may offer an objective biomarker of schizophrenia and provide further insight as to how disruptions in gamma affect neuronal processing and behavior. ASSRs have also been used to help elucidate potential mechanisms by which hallucinations in schizophrenia are associated with phase synchronization between the primary auditory cortices (Mulert et al., 2010).

4. Preclinical models of EEG abnormalities

4.1 Approaches to modeling EEG in mice

Historically, EEG and ERPs have been most commonly obtained from deeply anesthetized animals. In such preparations, the animal is typically placed within a stereotaxic apparatus and surgical procedures are used to remove the skull and expose the brain. A recording electrode is then lowered into the appropriate location in the brain and recordings are obtained. Typically, auditory stimuli are delivered through speakers located in the stereotaxic apparatus. There are several advantages to the use of this methodology. First, since the electrode is not permanently affixed to the skull, it can be moved around so as to obtain the best signal possible. This is especially true if the researcher is interested in obtaining ERP/EEG recordings within cell populations that can be easily identified according to a unique firing pattern. Second, since the auditory stimulus is presented at a

very short and invariant distance from the auditory canal, the resulting EEG response will typically show low levels of variance across trials and across different animals, leading to very stable and reliable results. Third, since the animal is anesthetized the EEG/ERP is less likely to be influenced by such factors as state of arousal, movement or attention to extraneous stimuli. While less popular in recent years, this methodology is still widely used within some research communities and is especially useful when one is interested in studying EEG and electrophysiology primarily as an end in itself. A major drawback to recording EEG in this manner lies in the limited translatability to the types of EEG methodologies used in patient populations. If this is a goal of the study, recording EEG in awake and freely moving animals is the more optimal choice. While the results obtained using this methodology can indeed be confounded by extraneous factors, such factors may actually be useful to study within the context of translational research. For example, changes in arousal can occur following exposure to drugs that stimulate nicotinic receptors and EEG techniques could be used to examine the neural processes responsible for this change. It should be noted that these two techniques can produce very different results under some circumstances. For example, amphetamine increases theta oscillations in anesthetized animals, but decreases theta in awake animals. This difference could be due to the fact that the inherent state of arousal is greatly different in the two cases, or could be due to the locomotor enhancing effects of amphetamine, which could act to increase movement related theta in awake but not anesthetized animals.

A second consideration involves the question of electrode placement. In some cases, EEG and ERPs can be obtained from electrodes placed on the scalp (in humans) or the surface of the cortex (in animals). Alternatively, electrodes can be placed within a particular region of the brain, such as the hippocampus, that the researcher may be interested in. Superficially, recording from the surface of the cortex offers the greatest similarity to the scalp recordings ordinarily obtained in human subjects and, thus, may be of greatest interest to researchers interested in translational studies. However, it should be noted that there is often little overlap in organization and topography between human and animal cortices, and this could lead to divergent or erroneous results. Similarly, since the relative size of the cortex is much smaller in animals and since electrical activity can carry over great distances in the brain it is quite likely that surface recordings in animals are strongly influenced by electrical activity occurring in sub-cortical areas. This is much less likely to be an issue in humans, given the much greater size of the cortex in this species. Traditionally, depth recordings have been the exclusive domain of animal researchers, due to the difficulty of obtaining depth recordings in human subjects (although such recordings have been obtained in humans during surgical intervention to reduce epileptic seizures). In general, depth recordings have been most widely used by researchers interested in studying the function of particular brain regions and offer a great opportunity to study neural activity within isolated brain regions. It should be noted that there are some EEG phenomena that are only see during depth recordings in isolated regions. A primary example of this is movement-induced increases in hippocampal theta, which are only observed when recording EEG directly in the hippocampus (Krause et al., 2003). Nonetheless, depth recordings offer many advantages over surface electrodes. First, since depth electrodes are located within the neural tissue, as opposed to being on top of the brain or on the scalp, signals obtained with depth recordings usually have much greater amplitude than those obtained from the surface. As a consequence, there is typically less variance across trials and across animals in depth recordings. Second, depth recordings

are less susceptible to the confounding effects of muscle activity or movement that often occur when recording from the scalp. Finally, due to the emergence of deep brain stimulation as a method to improve brain function in various disease states, it is becoming increasingly possible to record from within particular brain regions in humans as well, suggesting that the results from depth recordings done in rodents may become increasingly translatable to human studies (McCracken and Grace, 2009).

4.1.1 EEG from human to mouse

In addition to human studies, the neural information processing has been investigated with auditory evoked potentials in cats, rats, mice, and monkeys (Cook et al., 1968, Javitt et al., 1996, de Bruin et al., 1999, Javitt et al., 2000, de Bruin et al., 2001, Pincze et al., 2001, Ehlers and Somes, 2002). Rodents were shown to share many similarities with humans for specific portions of the ERP, including mouse analogs of the P50, N100, P200, and P300 components. These components are named the P20, N40, P80, and P120 in mice according to the time point the deflection takes place. They occur at approximately 40% of the latency of the human components and share similar overall morphology with the human components in response to parametric manipulation and pharmacological agents (Iwanami et al., 1994, Siegel et al., 2003, Hajos, 2006). The latency shift may be explained by the difference in brain size. As such, shorter distances allow faster progression of neural activity. However, the literature about the analogy of humans and rodent ERP is controversial and highly debated (Ehlers et al., 1997, Miyazato et al., 1999).

4.1.2 Mouse correlates of the human ERP waveform

The human P50 component is a positive deflection that occurs approximately 50 milliseconds following the onset of sensory stimulation. Mice show a similar early positive ERP component that emerges roughly 20 milliseconds after stimulus onset (Siegel et al., 2003, Maxwell et al., 2004, Umbricht et al., 2004). The mouse P20 shows a number of similarities to the human P50, including inter-stimulus interval (ISI) and intensity functions (Onitsuka et al., 2000, Maxwell et al., 2004), as well as pharmacological response to a wide variety of agents including amphetamine, ketamine, nicotine and neuroleptics (Stevens et al., 1995, Maxwell et al., 2004, Halene and Siegel, 2008, Rudnick et al., 2009). These factors have led to the suggestion that the P50 could potentially serve as a useful biomarker for detecting disease presence and for assessing treatment response. Several studies have shown correlations between reduced P50 (gating and amplitude) and impaired performance on measures of sustained attention and speed of processing (Cullum et al., 1993, Erwin et al., 1998, Potter et al., 2006, Smith et al., 2010). Decreases in P50 gating and amplitude are related to reduced working memory performance in schizophrenia (Cullum et al., 1993, Smith et al., 2010). Furthermore, mice show a negative deflection in the ERP around 40 milliseconds that shares a remarkable similarity with the human N100. For example, both the mouse N40 and human N100 show decreased amplitude during acute exposure to ketamine (Maxwell et al., 2006a, Murck et al., 2006, Lazarewicz et al., 2010). Furthermore, the mouse N40 has been shown to be sensitive to changes in stimulus novelty (MMN). Ketamine administration attenuates this sensitivity (Siegel et al., 2003, Ehrlichman et al., 2008).

Following the N100, the human ERP contains a second positive deflection termed P200. Mice show a clear P200-like response that appears around 80 milliseconds following

stimulus onset. Several lines of evidence have proposed a relationship between the mouse P80 and cognitive function. Example given, P80 amplitude and gating are reduced in mice exposed to ketamine but are increased following nicotine treatment (Connolly et al., 2004, Amann et al., 2009). The P300 component is seen during cognitive processing of stimuli or during departures from a frequently occurring stimulus (Linden, 2005). Corresponding to the human P3a, an augmentation in the mouse P120 has been shown following a novel stimulus (Siegel et al., 2003). However, there has not been a clearly defined demonstration of a P3b-like response in rodents. The lack of evidence for a P3b type component in rodents may be due to fact that the methodology required to produce such a response has not been pursued (Figure 1).

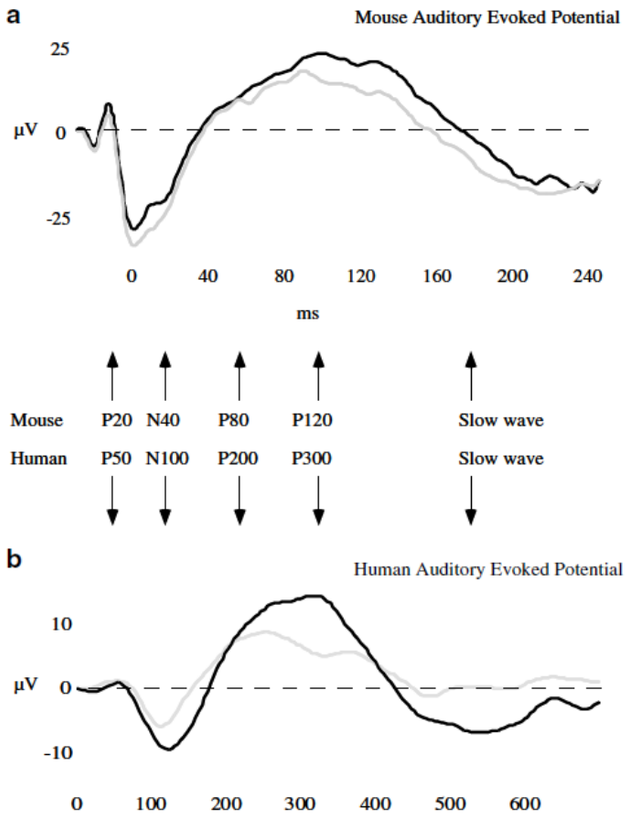

Fig. 1. (a) Mouse ERP to novel (black) and standard (gray) across all strains and drug treatment conditions. (b) Human ERP responses to novel (black) and standard (gray). Note that the human P300 and mouse P120 display increased amplitude following novel stimuli. As in Figure3, the timescale for mice is 40% that in humans and the amplitude of evoked potentials is greater in mice due to the use of intracranial electrodes as compared to scalp electrodes in humans. Reproduced with permission from Siegel (Siegel et al., 2003).

Mismatch negativity is elicited when the monotony or repetitive stimulation is interrupted by a deviant stimulus. Although deviant stimuli result in ERPs with similar morphology to that elicited by the repetitive stimulus, the negative deflection is enhanced in amplitude and latency. While mismatch negativity is simple to evoke and constitutes a robust finding in humans, dichotomy exists between the studies in rodents. The most contentious point is the

existence of MMN in mice. As the human MMN temporally follows the N100, the MMN-like activity in rodents appears as a negative deflection after the N40 component. Furthermore, similar to human, ketamine abolished the generation of MMN-like activity in mice (Ehrlichman et al., 2008). However, mismatch negativity-like activity observed in mice generates an ERP with increased amplitude in N40, but contradictory findings of the latency changes exits. Among others, Sambeth and Ruusuvirta did not observe any significant differences in the deviance-related activity compared to the standard-related activity (Ruusuvirta et al., 1998, Sambeth et al., 2003). However, a number of other studies have confirmed the presence of evoked potential components that are similar to MMN observed in humans (Ehlers and Somes, 2002, Siegel et al., 2003, Umbricht et al., 2005). Umbricht demonstrated that the deviant manipulation (e.g., frequency, probability, duration) has to be well chosen in that only deviants differing in stimulus duration from standard stimuli were shown to successfully induce the MMN in mice. Alternatively, Ehrlichman and others have shown frequency elicited MMN in mice (Ehrlichman et al., 2009a). In summary, although several approaches in mouse have succeeded to induce ERP activity corresponding to the human MMN, further studies are needed to establish this endophenotype as a robust model.

4.2 Model systems

Animal models are extremely useful and serve as an essential tool for investigating mechanisms and treatments for a variety of human disorders including schizophrenia.

Similar to human evoked-potential studies, rodents can be examined for endophenotypes of pre-attentive auditory processing, the ability to discriminate between tones presented at different frequencies or temporal proximity. Auditory evoked responses have been extensively explored in rats and mice (Simpson and Knight, 1993, Siegel et al., 2003, Umbricht et al., 2004), with highly analogous waveforms observed across species. The following section provides an overview of currently used approaches to model particular aspects or endophenotypes of schizophrenia, highlighting the advantages and limitations of each model. In particular, transgenic, pharmacological, and environmental models are reviewed.

4.2.1 Pharmacological approaches

Pharmacological models of schizophrenia are based on the current understanding of the alterations in various neurotransmitter systems. They rely on the observation that certain drugs induce prominent behaviors and features mimicking aspects of schizophrenia. The lack of efficacy for antipsychotics with respect to negative symptoms and cognitive deficits is a significant obstacle for the treatment of schizophrenia. Developing new drugs to target these symptoms requires appropriate neural biomarkers that can be investigated in model organisms, be used to track treatment response, and provide insight into pathophysiological disease mechanisms.

This section reviews the extent to which EEG studies in pharmacological model systems have helped to understand the contributions of dopamine, glutamate (e.g. NMDA receptors), and nicotine in both disease and therapy.

Dopamine. Schizophrenia has traditionally been linked to dysfunctional dopamine neurotransmission (Carlsson, 1977, Bennett et al., 1998). The dopamine hypothesis postulates dopaminergic hyperfunction in schizophrenia. Among other neurotransmitters,

dopamine is involved in the sensory gating (Javanbakht, 2006). For instance, the indirect dopamine agonist, amphetamine, produces a psychotic state in healthy individuals and exacerbates the symptoms of psychosis in patients (Angrist et al., 1970, Levy et al., 1993). Amphetamine became one of the most used models for schizophrenia, largely because it reproduces fairly well positive symptoms (e.g., hallucinations, paranoia, and psychosis) in humans. In addition to studies in humans, auditory gating has also been frequently demonstrated in laboratory animals (Shaywitz et al., 1976, Adler et al., 1988, Stevens et al., 1991). As such, amphetamine-induced alterations of the auditory processing abnormalities common to schizophrenia are well characterized in rodents and applied in multiple studies to investigate the amphetamine effect on rodent ERP. It has been repeatedly reported that amphetamine significantly disturbs ERP amplitude and gating, in particular diminishing N40 and P80 components (Stevens et al., 1991, Stevens et al., 1996, de Bruin et al., 1999, Maxwell et al., 2004). Furthermore, normal gating in rats is disrupted following amphetamine administration. Decreased N50, the rat correlate of the human P50, amplitude and abolished suppression of the neural response to the second stimulus resemble the gating disturbances seen in acutely psychotic, unmedicated patients (Adler et al., 1986). Ehrlichman and colleagues found amphetamine to reduce theta power following a stimulus which is consistent with other animal models and also with studies in humans suffering from schizophrenia (Yamamoto, 1997, Koukkou et al., 2000, Krause et al., 2003, Ehrlichman et al., 2009a). However, amphetamine did not significantly change basal power (theta, gamma) and evoked gamma power which is inconsistent with common findings in schizophrenia. Suggesting, while dopamine plays a key role in the generation of theta oscillations, its involvement in generating gamma oscillations is marginal (Kocsis et al., 2001, Kirk and Mackay, 2003). Amphetamine has been a heuristic model of positive psychosis fundamental to schizophrenia. However, amphetamine poorly mimics negative and cognitive symptoms of the disorder (Angrist et al., 1974). Moreover, chronic, stabilized patients generally exhibit a diminished response when exposed to amphetamine and also of the show a paradoxical behavioral improvement (Kornetsky, 1976, Angrist et al., 1982). Consequently, amphetamine has been proposed to constitute a model of positive psychosis in general, not specifically to schizophrenia. Finally, increased dopamine activity seems to play a limited role in the generation of negative and cognitive symptoms. Conclusively, amphetamine-treated animals provide only a limited representation of the traits of schizophrenia (i.e., positive symptoms).

Glutamate. Considerable evidence implicates reduced glutamatergic N-methyl-D-aspartate receptor (NMDAR) mediated signaling as the core pathophysiologic deficit of schizophrenia (i.e., the Glutamate Hypothesis) (Goff and Coyle, 2001, Coyle, 2006). Pharmacological evidence emerges from the effects NMDA receptor antagonists such as PCP, ketamine, and dizocilpine (MK801). Specifically, in healthy subjects aforementioned NMDAR antagonists were shown to induce a transient state characterized by symptoms associated with schizophrenia (Pearlson, 1981, Krystal et al., 1994). NMDAR antagonists as model of schizophrenia became of great interest because these antagonists cover the complete spectrum of symptoms: 1) positive (paranoia, agitation, and auditory hallucinations), 2) negative (apathy, though disorder, social withdrawal) and 3) cognitive symptoms (impaired working memory) (Becker et al., 2003). NMDA receptor antagonizing drugs have also been reported to induce schizophrenia-like alteration of event-related potentials, such as reduced P300 and impaired MMN (Oranje et al., 2000, Umbricht et al., 2000). As reviewed above, NMDARs are critically involved in the generation of human MMN making them a fortiori

interesting as a target to model schizophrenia. In line with human studies, animals treated with NMDAR antagonists exhibit similar electrophysiological shifting. Taken together, all these aspects prompted researchers to increasingly employ pharmacological NMDAR blockade as a disease model (Olney et al., 1999). Thus, the following section reasons approaches using ketamine, PCP, and MK801 to model the glutamatergic theories of schizophrenia.

Patients treated with **ketamine** experience an exacerbation of positive and negative system, suggesting that NMDAR antagonists affect a brain system that is already vulnerable in schizophrenia (Javitt, 2010). Similar to healthy humans, animals treated with ketamine exhibit behavioral and electrophysiological features that closely resemble schizophrenia. Consistent with results in human, studies have demonstrated that acute ketamine administration decreases the amplitude and latency of the mouse N40 and P80 mimicking schizophrenia-like abnormalities on those components (Connolly et al., 2004, Maxwell et al., 2006a). However, a study by de Bruin and colleagues (de Bruin et al., 1999) reported that acute ketamine had no effect on gating of the N40 and P80 components. However, De Bruin confirmed that ketamine selectively decreased the amplitude of P80 in awake rats (de Bruin et al., 1999). Furthermore, mice undergoing 14 days of chronic ketamine (daily acute administration) showed lasting effects of long-term ketamine exposure such as decreased N40 amplitude (Maxwell et al., 2006a). Reduced ability to detect changes in the auditory environment is a further characteristic of schizophrenia which can be addressed by administering ketamine to rodents. Ketamine has been reported to impair gating of responses to repeated clicks presented at 100ms intervals (Boeijinga et al., 2007). While some studies have reported ketamine to disrupt MMN (Connolly et al., 2004, Bickel and Javitt, 2009, Ehrlichman et al., 2009a), others observed no significant effects (de Bruin et al., 1999, Connolly et al., 2004, Heekeren et al., 2008). In animals, ketamine disrupted the auditory gating and MMN with deficits similar to those seen in schizophrenia (Miller et al., 1992, Tikhonravov et al., 2008). Thus, deviance-elicited changes in N40 amplitude and in the subsequent temporal region between 50-75 msec (late N40 negativity) are observable, which displays characteristics similar to those seen with MMN in humans. Ehrlichman and others have found that ketamine attenuates both of these responses (Ehrlichman et al., 2008). These findings are important for several reasons. (1) They bolster the link between deviance detection and the NMDA receptor system. (2) They support the hypothesis that mouse N40 is the analogous to the human N100 which finally (3) demonstrates the feasibility of ketamine as a NMDAR antagonist to be a model of schizophrenia. Using the auditory click paradigm, Lazarewicz and others investigated the effect of ketamine on background, evoked, and induced power (Lazarewicz et al.). While low dose of ketamine (5mg/kg) only affected background power in the theta range, the higher dose (20mg/kg) significantly increased background power in theta and gamma range. Additionally, they observed a decrease in evoke theta power (3-12Hz) and an increase in evoked gamma power. Similar findings were replicated in rats as well as in humans (Hahn et al., 2006, Hong et al.). The reports of gamma power abnormalities highly diverge. Reduction on gamma power and synchronization are frequently reported in schizophrenia (Haig et al., 2000, Gallinat et al., 2004, Uhlhaas and Singer). However, inconsistent data exist (Lee et al., 2003, Spencer et al., 2003). Acute brain slice preparations have also been used to investigate gamma synchrony in pharmacologic models of schizophrenia. Such paradigms have demonstrated strikingly divergent results from the in vivo studies described above. Whereas in vivo studies

demonstrated consistent brain-region independent increases in gamma activity with ketamine, slice studies reported increased gamma power only in auditory cortex with no changes in other cortical regions.

Phencyclidine (PCP) and other dissociative PCP-like drugs (e.g., MK801) are extensively applied to model schizophrenia, in particular due to its ability to mirror the symptomatology of schizophrenia including positive, negative, and cognitive symptoms (Bodi et al., 1959, Javitt et al., 1987). Especially, psychosis induced by PCP gained great interest since it reflects fairly well clinical features of the schizophrenia psychosis. Rats exposed to acute PCP display an impaired sensory gating, in particular of N2. Furthermore, Dissanayake and others found PCP to disrupt the gating of N2 in cortical and hippocampal areas (Miller et al., 1992, Mears et al., 2006, Dissanayake et al., 2009). Clozapine, an atypical neuroleptic, prevented the disruption in gating which stands in agreement with human studies demonstrating successful reversal of sensory gating deficits in schizophrenia (Nagamoto et al., 1996, Adler et al., 2004). Furthermore, schizophrenia-like abnormalities in MMN generation have been demonstrated by exposing monkeys to PCP (Javitt et al., 2000). Notably, PCP inhibited the N1 and P1 generation at long inter-stimulus-intervals (ISI), while at short ISI their generation was unaffected. Further, phencyclidine increases gamma frequency power, in particular in the hippocampus (Ma and Leung, 2000). Furthermore, an elevation in hippocampal theta power is observable following PCP administration. In contrary, total cortical power was reported to be decreased. Perinatal PCP exposure was found to result in long-lasting deficits in sensory gating, cognitive, and executive functioning in adult mice. Furthemore, atypical antispsychotics reverse these impairments. These biochemical and behavioral changes phenotipically resemble observations seen in schizophrenia and may serve as a model of the development of schizophrenia (Broberg et al., 2008, Wang et al., 2008).

Finally, **Dizocilpine (MK801)** is frequently used as an animal model of schizophrenia (Fletcher et al., 1989). However, in human research ketamine/PCP are used instead of MK801 due to its severe neurotoxicity. A single injection of MK801 is sufficient to model positive and negative symptoms. Animals treated acutely with MK801 mimic successfully the features of psychosis. Higher doses of MK-801 produce changes in brain activity accompanied by strong behavioral effects involving impaired locomotor control (Kovacic and Somanathan). Specifically, MK801 significantly augments low frequencies (1-6Hz) in cortical and amygdalar areas, while it concomitantly reduces higher frequencies (16-32Hz) (Ehlers et al., 1992). Also, the deficit in P200 gating seen in schizophrenia can be mimicked in the mouse correlate P80 by administrating MK801 (Ehlers et al., 1992). Finally, MK801 was shown to dose-dependently block the generation of MMN in unanesthetized monkeys and anesthetized rats (Javitt et al., 1996, Tikhonravov et al., 2008).

In summary, pharmacological approaches targeting NMDAR are effective tools in examining the pathophysiology of schizophrenia. Compared to other pharmacological animal models of schizophrenia, the NMDAR antagonist model provides clinical parallels allowing researchers to translate findings and treatment strategies from animal into human studies. A further advantage is the fact that acute exposures of above reviewed NMDAR antagonist induce schizophrenia-like symptomatology in healthy individuals lasting several hours up to days (Bakker and Amini, 1961). However, NMDAR antagonists produce acute receptor hypofunction and therefore fail to reflect chronic, developmental disruption in glutamatergic signaling that may underlie schizophrenia pathogenesis. Collectively, these virtues exemplify reasons for NMDA model in providing useful strategies to identify neural

endophenotypes in regard to development of new therapies to target treatment-resistant symptoms.

Nicotine. Nicotine has generated interest as a candidate for therapeutic use in alleviating schizophrenia symptoms. Individuals with schizophrenia are three times more likely to smoke and have high nicotine dependence compared to the general population (Hughes et al., 1986, de Leon and Diaz, 2005). They also have lower smoking cessation rates and self-administer more nicotine during cigarette smoking than control patients, a finding supported by measuring cotinine, a nicotine metabolite used as a biomarker of tobacco exposure (Olincy et al., 1997, de Leon and Diaz, 2005). This, along with the known prevalence of genotype differences leading to the loss of function in the alpha 7 nicotinic receptor found in individuals with schizophrenia, (Adler et al., 1998, Leonard et al., 2001, Picciotto and Zoli, 2008) supports the idea that individuals with schizophrenia self-administer nicotine as a form of self-medication to rectify deficits in neurocognitive performance and alleviate symptoms associated with the disease (Dalack and Meador-Woodruff, 1996, Kumari and Postma, 2005, Kumari et al., 2006)(Dalack and Meador-Woodruff, 1996).As mentioned previously, individuals with schizophrenia exhibit a higher ratio between the second and first stimulus in the auditory gating paradigm reflecting a dysfunction in stimulus processing. Acute nicotine in humans transiently normalizes the P50 gating deficit. This is observed with cigarette smoking in schizophrenia patients (Adler et al., 1993)as well as in studies using nicotine-containing gum in non-smoking family members of schizophrenia patients who exhibited P50 gating deficits (Adler et al., 1992). Mice undergoing 14 days of chronic nicotine increased both in the amplitude and gating of the P20, while having only acute nicotine decrease the amplitude and gating of N40(Metzger et al., 2007). A variety of pharmacological models further demonstrate the importance of the nAChr in stimulus gating. nAChR agonists display similar affects to nicotine. Acute administration of DMXB-A, a nicotinic agonist specifically targeting the alpha7 nicotinic, significantly suppressed the P50 of the test stimulus in subjects with schizophrenia, bringing the gating of the schizophrenia patients into the range of controls (Meyer et al., 1997, Olincy et al., 2006). These results were consistent with animal model studies testing the same drug(Stevens et al., 1998). Administration of 5-I A-85380, an alpha4beta2 nAChR agonist, in DBA/2 mice also significantly reduced the second to first stimulus response ratio (Wildeboer and Stevens, 2008). Tropisetron, a partial alpha7 agonist significantly improves gating in schizophrenia patients (Koike et al., 2005). Luntz-Leybman (Luntz-Leybman et al., 1992) showed that alpha-bungarotoxin, an alpha-7 nAChR antagonist, disrupts P20 and P40 gating in rats while mecamylamine showed no affect. Physiostigmine, a drug that deters the breakdown of endogenous cholinergic drug in the body by inhibiting acetylcholinesterase, normalizes P50 gating in a schizophrenia-free individual that exhibited gating deficits in the P50 gating, further supporting nicotine's role in modulating sensory gating (Adler et al., 1992). Direct pharmacological targeting of the nAChR directly is not necessarily the only way to trigger the receptors effects. In animal models, Siegel demonstrated that dopamine reuptake inhibition and nicotine antagonism both contribute to the observed phenotype of gating impairment in both the P20 and P40 gating in mice (Siegel et al., 2005). Nicotine and haloperidol increased P20 amplitude, supporting a role for nicotine agonists in pre-attentive sensory encoding deficits. While it remains elusive, the mechanism of action underlying the gating difference could be critical to understanding and treating the physiological

disturbances that cause the phenotype of schizophrenia, and nicotine is shown to affect this mechanism.

Since MMN deficits are thought to indicate degraded auditory perception experienced by schizophrenia patients, it follows that the effect of nicotine administration on schizophrenia symptoms be assessed using this measure. In the schizophrenia-free population, nicotine has been shown to enhance MMN amplitudes and shorten MMN latencies (Inami et al., 2005, Martin et al., 2009). Further evidence for the role of nicotine in ameliorating the MMN deficit emerges from the administration of the nicotinic agonist AZD3480, selective for the alpha-4-beta-2 subtype. As such, AZD3480 significantly increases the MMN amplitude and reduces the MMN latency, at the same time significantly enhancing scores in cognitive tests of attention and episodic memory when administered chronically for ten days (Dunbar et al., 2007). Human studies directly assessing the effects of nicotine on individuals with schizophrenia are few in number and exhibit mixed results. Acute nicotine transiently normalized the amplitude of MMN in response to duration but not frequency changes in auditory stimuli (Dulude et al., 2010). Inami found that acute transdermal nicotine in non-smokers reduces the MMN latency in healthy subjects, but not in patients with schizophrenia (Inami et al., 2007). This finding could be unique to the schizophrenia population that refrains from smoking and may reflect either differential drives to smoke based on symptom alleviation or be affected by the myriad of neuronal adaptations that chronic nicotine exposure induces, creating two distinct populations in schizophrenia. More studies are needed to elucidate the role of nicotinic receptors on MMN performance. There are several issues that limit nicotine being used as therapeutic drug. The ubiquity of nicotine receptors in the CNS and PNS make it difficult for a drug to target a specific region of the brain. A therapeutic drug's binding specificity and route of administration would therefore have to be optimized so as to minimize drug side affects. Nicotine itself has a short half-life. The rapid metabolism of the drug and its transient effects would mean that a mechanism of sustained release would need to be employed for the agent to remain active for an extended period of time. However, a direct impediment to this therapeutic modification is that nicotinic receptors exhibit quick desensitization. This would mean target receptors might not be available for binding and drug efficacy. These factors must be addressed before nicotine can be seriously considered as a candidate as a therapeutic drug for schizophrenia patients. There are currently several drugs that act at the nAChR that show promise. Agonists like DMXBA have been shown to successfully overcome several of these pharmacological challenges and stand as contenders for therapeutic relief (Martin and Freedman, 2007). Other options include the use of a positive allosteric modulator to enhance the efficacy of the receptor without directly activating it (Gronlien et al., 2007).

4.2.2 Transgenic approaches

Schizophrenia carries an important genetic contribution with a heritability of approximately 80% (Sullivan et al., 2003). ERPs deficits, particularly of the P50, N100, P300 and MMN components are among the most heritable (approximately 70%) and reproducible phenotypes of schizophrenia (Frangou et al., 1997, Ahveninen et al., 2006, Hall et al., 2006, Turetsky et al., 2007a). Whereas the number of candidate genes for schizophrenia is estimated to be over 1000, a subset of specific genetic contributions have been directly associated with ERPs. These genes are mostly involved in dopaminergic, nicotinic and glutamatergic mechanisms. For example, P50 gating deficits have been linked to the alpha-7

nicotinic acetylcholine receptor as well as the Catechol-O-methyltransferase (COMT) genes (Lu et al., 2007), although the later result was not replicated in a recent study (Shaikh et al., , Freedman et al., 1997, Leonard et al., 1998, Shaikh et al., 2011). Also, P300 amplitude decrease is associated with COMT and Disrupted in schizophrenia-1 (DISC1) genes while P300 increased latency is significantly influenced by the dopamine D2/D3 receptor as well as the Neuregulin-1 (NRG1) genes (Hill et al., 1998, Anokhin et al., 1999, Blackwood et al., 2001, Gallinat et al., 2003, Blackwood and Muir, 2004, Berman et al., 2006, Mulert et al., 2006, Bramon et al., 2008). Finally, whereas MMN is most extensively investigated in regard to glutamatergic mechanisms, no study has genetically linked both. However, a genetic association between MMN and the COMT gene has been shown (Baker et al., 2005). Those reports, combined with the aforementioned pharmacological studies, demonstrate the importance of investigating ERPs in specific transgenic (Tg) mouse models of schizophrenia. To date, the Tg mouse models that have been used to study ERPs components can be separated in 3 main groups based on the molecular pathway in which the target gene is involved: 1) Dopamine (COMT and G_sa Tg mice), 2) glutamate (NRG1 and NMDA receptor-1 (NR1)) Tg mice and 3) nicotine (C3H α7 receptor Tg mice).

Dopamine. *COMT Tg mice:* The Catechol-O-methyltransferase (COMT) is a key regulatory enzyme that degrades dopamine and thus controls dopamine availability (Axelrod and Tomchick, 1958, Goldberg and Weinberger, 2004). In humans, a single nucleotide polymorphism leads to the substitution of a Valine in place of a Methionine at the 158/108 locus (Lachman et al., 1996). This modification results in a two-fold increase of its activity thereby reducing dopamine levels (Chen et al., 2004). A recent study from our laboratory using COMT-Val-tg mice (Papaleo et al., 2008) shows a lack of change in P20 amplitude but a trend of P20 latency increase (unpublished data). These results are consistent with the human data mentioned above, which show both significant and non-significant genetic linkage between the COMT gene and P50 gating deficits. We also observed increased N40 latency and decreased P80 amplitude as well as reduced baseline theta and gamma power.

G_sa Tg mice: G_sa Tg mice express an isoform of the G-protein subunit G_sa that is constitutively active due to a point mutation (Q227L) that prevents hydrolysis of bound GTP (Wand et al., 2001, Gould et al., 2004). G_sa Tg mice displayed decreased amplitude of cortically-generated N40 that is reversed by the Gi-coupled dopamine D2-receptor antagonist haloperidol (Maxwell et al., 2006b). This result is consistent with the amplitude reduction of the N100 observed in patients with schizophrenia (Frangou et al., 1997, Ahveninen et al., 2006).

Glutamate. *NRG1 Tg mice:* NRG-1 is a high-risk gene for schizophrenia that has been associated with NMDA receptor hypofunction (Gu et al., 2005, Hahn et al., 2006, Bjarnadottir et al., 2007, Li et al., 2007). Although several Tg mice for NRG1 have been engineered, to our knowledge, only one study has tested auditory ERPs (Ehrlichman et al., 2009b). This study has used the NRG1 model in which all three major types of NRG1 have a partial deletion of the EGF like domain. These NRG1 heterozygote mice did not show deficits in P20 amplitude or gating. Nevertheless, they showed disrupted mismatch negativity similar to what is observed in schizophrenia. It would be interesting to investigate ERPs in the other NRG1 Tg mouse lines as it may help to identify which form of NRG1 mutant are most closely associated with the electrophysiological abnormalities commonly found in schizophrenia.

NR1 Tg mice: NR1 hypomorphic mice express 5-10% of the normal NR1 protein (Mohn et al., 1999). Several studies have reported behavioral abnormalities in these mice that are also found in schizophrenia. Since then, NR1 hypomorphic mice have been considered as a translation model for the disease. Measure of auditory and visual event related potentials showed significant increased amplitudes of P20 and N40 in NR1 hypomorphic mice, suggesting decreased inhibitory tone (Bodarky et al., 2009, Halene et al., 2009). Indeed, auditory gating for the P20 and the N40 peak is significantly impaired in these mice compared to their wild-type littermates (Bickel et al., 2007, 2008). Those results correlate with the pathophysiology of the observed gating and ERPs generation alterations in schizophrenia (Javitt et al., 2000).

Nicotine. *C3H α7 Tg mice* (Adams et al., 2008)**:** C3Há7 null mutant heterozygote mice exhibit significant reduction of the alpha-7 nicotinic receptor in the hippocampus. In these mice, the auditory gating for P20 and N40 was decreased compare to the wild type mice. This result is consistent with the deficit of P50 gating reported for schizophrenia patients. These data reinforce the idea of a genetic linkage between the alpha-7 nicotinic receptor and this phenotype observed in human.

4.2.3 Environmental approaches

The notion that schizophrenia occurs as a result of problems in neurodevelopment is strongly suggested by the appearance of a number of gross alterations in the brain inn schizophrenia, including enlargement of the cerebral ventricles, decreased cortical volume, and hippocampal cellular pathology (Harrison, 1999). That these alterations have occurred early in development can be assumed given that they occur largely in areas of the brain, such as the hippocampus, that complete the developmental process long before the typical onset of the disease. Although the full emergence of schizophrenia symptoms usually does not occur until late-adolescence or early-adulthood, people who subsequently go on to develop schizophrenia often show numerous deficits in cognitive and social function indicative of problems early in the developmental process. Given the importance of identifying the potential mechanisms that underlie such developmental changes, numerous neurodevelopmental models have been proposed in animals that presume to replicate the conditions leading to schizophrenia-like brain dysfunction.

NNVHL. Lesioning of the ventral hippocampal area during early life has been shown to reproduce in rodents many of the symptoms observed in schizophrenia. Important features of this model are: 1) post-pubertal emergence of behavioral changes 2) schizophrenia-like deficits in cognition 3) schizophrenia-like changes on putative positive symptom measures, such as amphetamine-induced locomotor activity and pre-pulse inhibition 4) schizophrenia-like cellular and neuroanatomical changes, including reductions in parvalbumin expressing GABAergic interneurons 5) exaggerated response to glutamate agonist and antagonists, suggestive of a hypoglutamatergic state. Importantly, most of these changes occur only when the lesion is induced during the neonatal period and do not occur in adult animals given similar lesions of the ventral hippocampus, suggesting that it is the altered neurodevelopmental environment that is the source of the changes observed in the model.

Methylazoxymethanol. Embryonic exposure to methylazoxymethanol acetate (MAM), an inhibitor of cell division, is currently a popular animal model of schizophrenia. Exposure to MAM at embryonic day 17 produces a pattern of brain atrophy in adult animals similar

to that seen in human schizophrenia (i.e. cortical and hippocampal atrophy) (Talamini et al., 1998). Importantly, these neural changes overlap with dysfunctions across a wide range of behavioral and cognitive domains known to be affected in humans with schizophrenia, including measures sensitive to mesolimbic dopamine function and cognitive performance. Thus, MAM treated animals display impaired long-term memory, working memory and attentional flexibility, as well as increased responsiveness to amphetamine as adults (Fiore et al., 2002, Gourevitch et al., 2004, Moore et al., 2006, Featherstone et al., 2007). The enhanced response to amphetamine is not seen when animals are tested during the pre-pubescent period, suggesting that the behavioral changes induced by MAM follow the same developmental time course seen in the human disease (Moore et al., 2006). Parvalbumin (PV) expressing GABAergic interneurons are dramatically reduced in both the hippocampus and PFC following embryonic MAM treatment, suggesting that these cells may be especially vulnerable to the effects of MAM. Moreover, it is possible that the loss of such cells could be responsible for many of the cognitive and behavioral changes that occur following MAM treatment (Penschuck et al., 2006). For example, PV expressing GABAergic interneurons are known to be the primary source of high frequency gamma oscillations. In a latent inhibition procedure, MAM treated animals showed reduced gamma power during pre-exposure to a tone and this was shown to correspond with impaired development of latent inhibition (Lodge et al., 2009). In contrast, exposure to MAM did not alter activity in the lower frequency theta band, suggesting a high degree of specificity in the underlying change induced by MAM treatment. Additionally, MAM treated animals show an enhanced locomotor response to NMDA antagonists such as ketamine and PCP, and this also appears to correspond strongly and specifically with a reduced ability for these drugs to alter activity within the gamma frequency range. Both studies suggest that MAM treatment results in a decreased inhibitory tone consistent with the proposed role of GABAergic interneurons in inhibitory function.

4.3 Limitation and future models

ERPs and ERSPs have been widely used to examine neural activity in normal individuals and those suffering from schizophrenia. The high degree of similarity between the methods used to assess these measures in humans and laboratory animals has made these techniques very valuable for studying normal and abnormal brain function. Presently, however, it is unclear how such measures relate to clinical symptoms or cognitive impairments, although evidence for a link between these measures and cognition is beginning to emerge. Future studies will need to assess the degree to which ERP and EEG measures relate to cognitive performance on tasks in mice that more closely replicate those used in humans. Establishment of such a link could provide a novel means for assessing cognition in mice and for testing potential pharmaceutical interventions for schizophrenia. Much work has been done assessing EEG during cognitive performance in humans, as well as in non-human primates, which has typically focused on sophisticated analyses of neural oscillations and synchrony. While such measures are interesting, ERP measures are also useful candidates for translational biomarkers of cognition, since they do not require extensive expertise to analyze and there are years of human data using these measures. Further, mice are excellent subjects for translational research, given the wide range of genetically modified mice available to researchers.

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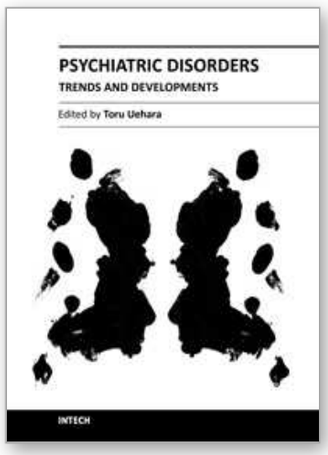

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Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, sever and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning is in some cases tragic. Aside from knowing the physical organic factors, such as infections, endocrinal illnesses or head injuries, the aetiology of psychiatric disorders has remained a mystery. However, recent advances in psychiatry and neuroscience have been successful in discovering subsequent pathophysiology and reaching associated bio-psycho-social factors. This book consists of recent trends and developments in psychiatry from all over the world, presented in the form of multifarious and comprehensive articles. The first two sections of the book are reserved for articles on schizophrenia and depression, two major illnesses present in this field. The third section of the book is reserved for addiction psychiatry, related not only to socio-cultural but also biological alterations. The last section of the book, titled Biological Neuropsychiatry, consists of three topics - updated molecular biology, fundamental neuroscience and clinical neuropsychiatric conditions. Doubtlessly, this book will be fruitful for future developments and collaboration in world psychiatry.

How to reference

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