5

Linking Stress and Schizophrenia: A Focus on Prepulse Inhibition

T.N. Douma[1,3], M.J. Millan[2], B. Olivier[1,3] and L. Groenink[1,3]
[1]*Div. of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht,*
[2]*Institute de Reserche Servier, Croissys/Seine,*
[3]*Rudolf Magnus Institute of Neuroscience*
[1]*the Netherlands*
[2]*France*

1. Introduction

Schizophrenia affects about 0.5-1.0% of people worldwide, occurring roughly equally in both men and women. The exact causes of schizophrenia are not fully understood, although the consensus of current research is that schizophrenia is a developmental disorder, caused by a genetic liability interacting with environmental and psychosocial stress. However, the possible neurobiological mechanisms underlying this gene-stress interaction are largely unknown.

To study the role of stress in the development of schizophrenia, it is useful to dissect this complex disease into specific symptoms. In this respect, a well-accepted model for psychotic-like behavior is prepulse inhibition (PPI) of the startle response. In an attempt to clarify the link between stress and schizophrenia, this chapter reviews experimental studies that determined the effect of acute and chronic stressors on PPI in humans and rodents. In section 2, studies that have focused on stress in adulthood will be discussed, and in section 3, studies that have addressed effects of early-life stress on PPI will be outlined. Together, the findings of these PPI studies support the neurodevelopmental theories of schizophrenia, which state that insults, including stress, experienced during early brain development could particularly increase the risk of developing schizophrenia.

1.1 Symptom dimensions in schizophrenia

Schizophrenia is a mental disorder, characterized by a mixture of symptoms that are generally divide into three major clusters: positive, negative, and cognitive symptoms (APA, 2000). The first category signifies symptoms that reflect excess in normal function, which comprises psychotic symptoms. These mental phenomena are often dramatic; the patient appears to have lost contact with reality. Hallucinations are one type of positive symptom; they are perceptions disconnected from external stimuli, which may occur in any sensory modality, however, auditory hallucinations (i.e. hearing voices) are the most common hallucinations in schizophrenia. Delusions are another type of positive symptom, which are fixed, false beliefs that are not shared by other people in the patient's neighborhood. The most common form is the paranoid delusion, such as the false belief that one is spied on, or

being persecuted. However, a variety of other themes is also possible, for instance the belief that the fillings in one's teeth are radio transmitters receiving extraterrestrial messages, or the belief that some outside agency has added or removed thoughts in one's brain.
Negative symptoms, on the contrary, describe loss or significant impairment of normal psychological functions, such as blunted affect, emotional withdrawal, poor rapport, passivity and apathy, and anhedonia (APA, 2000). Although this reduction in normal functioning may seem less dramatic as positive symptoms, particularly negative symptoms are associated with long periods of hospitalization and poor social functioning. Indeed, a patient's degree of negative symptoms appears to determine whether a patient is still able to function in society. Last, cognitive symptoms of schizophrenia comprise 'executive dysfunctions', including problems in maintaining goals, allocating attentional resources, evaluating and monitoring performance, and utilizing these capacities to solve problems.

1.2 Diathesis-stress hypothesis of schizophrenia

Schizophrenia is a complex illness, and its possible causes are still subject of debate. However, according to a widely adopted view, both a biological predisposition, and exposure to environmental stress are necessary ingredients for schizophrenia to become manifest – the so-called diathesis stress model (Zubin & Spring, 1977). A classical example of the association between environmental stress and the risk of developing schizophrenia, comes from studies of the 1944-1945 Dutch Hunger Winter (Susser & Lin, 1992; Susser et al., 1996; Susser et al., 1998). In this discrete period during the Second World War, there was a serious decline in food intake in six cities of western Netherlands. Among people born in these cities between 1944 and 1946, the most exposed birth cohort (i.e., conceived at the height of the famine) showed a twofold and statistically significant increase in the risk for developing schizophrenia (Susser & Lin, 1992). Since this particular famine, many others occurred worldwide, but these were less suitable for epidemiological investigations due to more disorganized conditions (St Clair et al., 2005). However, several years after the Dutch Hunger Winter, a similar occasion occurred in China. Specifically, from 1959-1961, people in affected provinces were starving and died in large numbers due to bad weather (for refs see (St Clair et al., 2005)). Among births that occurred during the famine years, the risk of developing schizophrenia in later life was significantly increased when compared to those born before or afterwards (St Clair et al., 2005).
These 'natural experiments' suggest that prenatal stress, i.e., exposure to maternal nutritional deficiency, could increase the risk of schizophrenia in later life. However, evidence from many observational studies that have investigated the association between experience of stress in adulthood and acute onset of psychotic illness, has not been confirmative (Phillips et al., 2007). In particular, there is no consistent evidence that experience of stressful life events is able to trigger onset of psychosis. Findings from longitudinal studies on the other hand, are stronger in linking episodes of relapse in schizophrenia patients to an elevated rate of stressful life events (Phillips et al., 2007; Walker et al., 2008), thus providing additional evidence for a role of stress exposure in (the course of) schizophrenia.

1.3 Neurodevelopmental hypothesis of schizophrenia

As mentioned earlier, schizophrenia is generally not diagnosed before the third decade of life, suggesting that it is the end point of some pathological process acting on the immature

brain. This observation has led to the formulation of the neurodevelopmental hypothesis of schizophrenia, which states that environmental disturbances during early brain development influence risk of developing schizophrenia (Harrison, 1997; Rehn & Rees, 2005; Fatemi & Folsom, 2009). Some candidates for these early disturbances are, for instance, prenatal influenza exposure, obstetric complications, prenatal maternal psychological stress, maternal and fetal nutritional deficiency, season of birth (for refs, see (St Clair et al., 2005)). However, obviously, not every individual will get ill if they experience stress. Consequently, it is thought that manifestation of disease originates through an interaction with the genetic make-up of an individual (Harrison, 1997; Rehn & Rees, 2005; Fatemi & Folsom, 2009). Several lines of evidence support the neurodevelopmental hypothesis, including epidemiological studies, premorbid history and neuropathological postmortem studies (Fatemi & Folsom, 2009). With respect to genetics, many susceptibility genes, found to be associated with a heightened risk for developing schizophrenia, have been linked to neurodevelopmental processes, such as synaptic connectivity, synaptogenesis, and growth factors (Stahl, 2008).

However, a remaining question is, whether one single intervention early in development is enough to explain occurrence of schizophrenia much later in life. An alternative hypothesis, that works within the framework of the neurodevelopmental theory, is referred to as the double-hit model (Keshavan & Hogarty, 1999; Keshavan, 1999; Maynard et al., 2001). According to this model, maldevelopment within 2 critical windows of vulnerability combines to lead to clinical manifestations of schizophrenia. First, early developmental risk factors (i.e. genetic predisposition, environmental stressor) will cause a heightened vulnerability to the illness through anomalous neural development and subtle changes in behavior. However, for schizophrenia to become manifest, an additional second hit (i.e. an environmental factor such as drug abuse or social stress) is considered necessary. Thus, in this view, early and late risk factors are not simply additive, but instead, the first hit will increase an individual's vulnerability for effects of a subsequent hit (Keshavan & Hogarty, 1999; Keshavan, 1999; Maynard et al., 2001).

1.4 Prepulse inhibition of the startle response

In order to test the above-mentioned theories, animal models could be used. However, due to the nature of the symptoms and the pathological complexity of schizophrenia, it is impossible to reproduce the disease in its entirety in an animal model. As a possible solution, one could model specific aspects or symptoms of the disorder. A highly validated model in this respect is the behavioral paradigm of prepulse inhibition (PPI) of the acoustic startle response, which is typically, but not exclusively, diminished in schizophrenic patients (Braff et al., 2001a; Geyer et al., 2001; Swerdlow et al., 2001; Swerdlow et al., 2008). As disrupted PPI is a trait marker of schizophrenia, which is also displayed by patients' unaffected relatives, as well as schizotypal (i.e., non-psychotic, unmedicated) patients, impaired sensorimotor gating is considered an endophenotype of schizophrenia (Braff et al., 2008).

PPI refers to the normal suppression of a startle response to a strong stimulus when it is preceded by a weaker stimulus (the prepulse). In rodents, PPI is commonly measured as whole-body startle responses, whereas in human experiments, generally eye-blink responses are used. In theory, deficient PPI in schizophrenic patients reflects a dysfunction in the gating of sensory and cognitive information, clinically manifesting as a patient's

inability to filter irrelevant thoughts and sensory stimuli from intruding into awareness (Braff et al., 1978; Braff et al., 2008). Some cross-sectional and longitudinal studies demonstrate that in patients, deficits in sensorimotor gating are improved by atypical antipsychotics (Swerdlow et al., 2008; Aggernaes et al., 2010). Neurophysiologically, PPI is mediated via the brainstem, whereas it is regulated by an extensive set of interrelated projections from the forebrain (Swerdlow et al., 2001). Pharmacological interventions that diminish PPI are well characterized in animal models (Geyer et al., 2001) and also increasingly applied in healthy human subjects (Braff et al., 2001b; Oranje et al., 2004; Jensen et al., 2007; Oranje et al., 2011). In particular, PPI is disrupted by dopamine receptor agonists (e.g., apomorphine), serotonin receptor agonists (e.g., 8-OHDPAT), and NMDA receptor antagonists (e.g., PCP). Accordingly, the different models of disrupted PPI have been used in the search of novel antipsychotic treatments, and each of the models has proven to be sensitive to at least some antipsychotic medications (Geyer et al., 2001). Notably, concerning interventions in the dopaminergic system, application of receptor agonists into the (subcortically located) nucleus accumbens and receptor antagonists in the medial prefrontal cortex diminish PPI (Wan & Swerdlow, 1993; Ellenbroek et al., 1998), providing considerable construct validity to PPI as a model for deficient sensorimotor gating in schizophrenic patients. Thus, PPI is considered a robust, predictable and neurobiologically informative experimental measure, broadly used in translational models for schizophrenia research. While PPI is largely determined by anatomical and genetic traits (Swerdlow et al., 2008), it may also be sensitive to effects of stress – which may be even more relevant, considering the leading theories on the development of schizophrenia. Therefore, the aim of this chapter is to explore the studies that applied experimental stressors to investigate their influence on PPI.

2. Adult stress and gating mechanisms: Evidence from animal and human studies

2.1 Effects of acute stress on sensorimotor gating: Animal studies

In this section, we will review the existing literature on the effects of acute and chronic stress on PPI in adult rodents. For this purpose, some studies have pharmacologically interfered with a neural system that is fundamental to the biological stress response in mammals, the hypothalamic-pituitary-adrenal (HPA) axis, as discussed in section 2.1.1. Alternatively, external stressors have been artificially applied to rodents in the laboratory. In general, these stressors can be classified as either physical (i.e., nociceptive) or psychological, which will be outlined in sections 2.1.2. and 2.1.3., respectively.

2.1.1 HPA modulators

In a straightforward approach to address the link between stress in adulthood and PPI, some studies have pharmacologically interfered with the HPA axis, a major mammalian stress system. Physiologically, the function of the HPA-axis is to transduce neural signals that arise in response to any physical or psychological stressor, into an endocrine response; starting at the level of the brain's major integrating center: the hypothalamus. In this structure, the neuropeptide corticotrophin-releasing factor (CRF) is produced. When CRF is released into the hypophyseal portal system, it travels to the pituitary gland, where it binds to CRF_1 receptors. This, in turn, triggers the secretion of adrenocorticotropic hormone

(ACTH). Subsequently, ACTH is transported via the systemic circulatory system to the cortex of the adrenals, where it triggers the release of glucocorticoids. Through a negative feedback at the level of the hypothalamus and pituitary, glucocorticoids (cortisol in primates and corticosterone in rodents) ultimately inhibit their own release. For decades, the HPA-axis has been linked to schizophrenia (Yeap & Thakore, 2005; Phillips et al., 2006; Phillips et al., 2007; Walker et al., 2008). Notable findings in patients are elevated cortisol levels, especially shortly before onset of psychosis (reviewed by Walker & Diforio, 1997; Walker et al., 2008), and altered stress responsiveness, with cortisol responses being both enhanced (Walker et al., 2008) and blunted (Brenner et al., 2009; van Venrooij et al., 2010).

Some experimental animal studies have investigated the influence of HPA-axis manipulations on PPI. For instance, Van den Buuse and co-workers investigated the effects of a dopaminergic D2 receptor antagonist (i.e. haloperidol) on the PPI response in mice following adrenalectomy and corticosterone replacement (2, 10 or 50 mg) (van den Buuse et al., 2004). Subsequently, the animals were tested for PPI after injection of haloperidol. In adrenal-intact mice and in mice implanted with 10 mg corticosterone, haloperidol treatment increased PPI, while in both the 2 and 50 mg corticosterone-adrenalectomy groups, PPI was unchanged. The authors explained their results by postulating a corticosterone-dopamine interaction; moderate levels of corticosterone would be needed for a normal dopaminergic tone, while both low and high concentrations of corticosterone would induce reductions in dopaminergic activity (Van den Buuse et al., 2004). Indeed, an interaction between corticosteroids and central mesolimbic dopaminergic activity is suggested by several studies (Piacentini et al., 2004; Pruessner et al., 2004; Marinelli et al., 2006).

At the level of CRF, intraventricular brain injections with the neuropeptide lead to reliable alterations in PPI. This is not surprising, given the putative involvement of CRF in stress disorders and psychosis (Nemeroff et al., 1984; Charney et al., 1993; Sautter et al., 2003; Herringa et al., 2006) and the fact that CRF receptors are expressed in areas that modulate startle and PPI, including brainstem, limbic and cortical nuclei (Van Pett et al., 2000). In rodents, both acute central administration of CRF (Conti et al., 2002; Risbrough et al., 2004; Conti, 2005; Bakshi et al., 2011) and chronic CRF overexpression (Dirks et al., 2002) diminish PPI. However, unlike central CRF, peripherally injected CRF at doses that are known to cause the release of ACTH and corticosterone, did not reduce PPI in rats (Conti, 2005). Consequently, it was suggested that the effect of central CRF on PPI might be independent of its effects on the HPA axis. This finding is in agreement with a study of Groenink et al. (2008), which showed that neither glucocorticoid receptor antagonists nor adrenalectomy did improve perturbation of PPI in mice overexpressing CRF (CRF-OE mice). In addition, elevation of corticosterone levels by pellet implantation did not affect PPI in wild-type mice. In contrast, two different CRF_1 receptor antagonists significantly restored PPI in CRF-OE mice, based on which the authors concluded that chronic overactivation of CRF_1 receptors rather than excessive glucocorticoid receptor stimulation underlies PPI deficits in CRF-OE mice. Also in rats, neither acute, nor repeated administration of corticosterone decreased PPI (Czyrak et al., 2003). In the brain, CRF acts via CRF_1 and CRF_2 receptors. Risbrough et al. (2004) investigated the respective roles of these two receptor subtypes in the startle response and sensorimotor gating in mice. Regarding the magnitude of startle, they found that CRF_1 receptors are required for the effects of CRF, and CRF_2 receptors appear to have an auxiliary role. Furthermore, CRF_1 receptor blockade reversed CRF-induced deficits in PPI, whereas CRF_2 receptor blockade potentiated the latter effect. In addition, CRF_2 receptor activation

increased PPI. Together, as was argued, these findings support the idea that CRF_1 and CRF_2 receptors exert opposing roles in inhibition of startle, with CRF_1 decreasing PPI and CRF_2 increasing it. Thus, the effect of central CRF on PPI is probably not mediated by corticosterone. However, as was mentioned before, corticosteroids could play a role in regulating PPI via an interaction with mesolimbic dopaminergic activity.

2.1.2 Physical stressors

From animal models, it has long been known that intermittent and inescapable foot-shock can induce a state of analgesia (stress-induced analgesia), which is reversed by the opiate receptor antagonist naloxone (Madden et al., 1977). Functionally, this anticipation response to upcoming aversive stimuli reduces their impact and is thought to help the organism cope with the stressor (Willer & Ernst, 1986). To examine whether exposure to a severe stressor induces changes in sensory functioning that accompany stress-induced analgesia, Leitner and co-workers measured PPI in rats shortly (i.e., 20 min) after exposure of cold swim stress (Leitner, 1986). Next to a reliable analgesia, the stressed animals exhibited decreased prepulse inhibition. In a subsequent study, this stress-induced PPI-deficit appeared to be of a multisensory nature, as reductions in PPI were found in reaction to both visual and acoustic prepulse stimuli (Leitner, 1989). The author interpreted these results as a general decrease in sensory sensitivity, which extends beyond the noxious stimulus (i.e., cold water). The finding supports a possible role for opiates in the PPI-disruptive effect of analgesia, in that opioid receptor agonists, which produce perceptual distortions in animals and humans, disrupt PPI in a dose-dependent fashion (Bortolato et al., 2005). However, another nociceptive stressor, i.e., repeated inescapable foot-shocks, slightly increases PPI (Pijlman et al., 2003), or has no effect (Bijlsma et al., 2010; Bakshi et al., 2011). Possibly, these conflicting findings can be partly explained by the longer stress-test intervals applied in the latter studies (see table 1). Lastly, the physical stressor referred to as restraint stress, comprises physically restraining a rodent in a narrow cylinder, usually for 15-20 minutes, sometimes on several subsequent days. Restraint stress has been shown to increase plasma ACTH, beta-endorphin, and corticosterone levels, and also brain levels of serotonin and norepinephrine (for refs, see (Acri, 1994)). However, the studies that examined the effects of restraint on PPI, have mostly reported inconsistent, or no effects of restraint (Acri, 1994; Faraday, 2002; Bijlsma et al., 2010), and one study showed that repeated, but not acute, restraint stress decreased PPI (Sutherland & Conti, 2011).

Thus, studies that have applied physical stressors in adult rodents have yielded inconsistent or no effects on PPI (table 1.a.). However, although some of these artificial stressors have been shown to be capable of producing elevated levels of stress hormones, the ethological validity of these stressors is not very high. In the next section, studies that examined the influence of ethologically more relevant psychological stressors will be discussed.

2.1.3 Psychological stressors

As opposed to physical stress, psychological stress does not involve a nociceptive component, as physical contact with the stressogenic stimulus is absent. This can be accomplished in several ways. One particularly simple method to induce emotional stress involves forcing rats to witness another rat being exposed to physical stress, such as repeated foot-shocks, or restraint. This observational stressor has been found to activate mesocortical dopamine systems (Kaneyuki et al., 1991). However, it is also proposed to

represent a milder form of stress, as plasma corticosterone levels were found to be less elevated, compared to the concomitant physical stress condition (Acri, 1994). Studies that examined sensorimotor gating following witness stress, have reported no effects on PPI (Acri, 1994; Pijlman et al., 2003).

Another psychological stressor, that is considered more potent, is referred to as social defeat. In this paradigm, an animal is made an intruder, by placing it into the residential cage of an aggressive conspecific, where it is attacked, though, generally, the experimenter will protect it from suffering too much physical harm. After a few minutes, the intruder is placed in a small cage within the resident's cage. As a consequence, it is not exposed to further injuries and direct attacks, but still remains in an unfamiliar environment, with olfactory, visual and to some extent physical (only via vibrissae) contact with the resident. Social defeat may have some face validity with respect to schizophrenia, as high levels of social competition and migration are proposed as risk factors for developing schizophrenia (Selten & Cantor-Graae, 2007). In rodents, social defeat has been associated with dopaminergic hyperactivity and to behavioral sensitization, whereby the animal displays an enhanced response to dopamine receptor agonists (Selten & Cantor-Graae, 2007). With respect to PPI, significant impairments in the response were found following 3 weeks of daily social defeat in adult mice, which could be normalized by acute treatment with the cannabinoid receptor agonist WIN55212.2 (Brzozka et al., 2011).

Another ethologically valid psychological stressor involves exposure to a predator. Next to foot-shock stress (see section 2.1.2), Bakshi and co-workers also exposed their rats to ferrets, one of their natural predators (Bakshi et al., 2011). To make sure that the stressor would be entirely psychogenic, the rats were protected from injury by a protective cage. This kind of predator exposure has been shown to elicit acute HPA axis activation, freezing behavior and ultrasonic vocalizations (for refs, see Bakshi et al., 2011). When compared to foot-shock stress, predator exposure was found to be equipotent in terms of the amplitude of acute corticosterone release. However, foot shock stress had no effects on PPI at any measured time-point, while predator exposure significantly disrupted PPI at 24 hours after the stress; but not acutely, or 48 hours, or 9 days later (Bakshi et al., 2011).

In our laboratory, we examined the influence of psychological stress, i.e., the potential threat of bright light, on PPI in Wistar rats. In rodents, high illumination potentiates startle (light-enhanced-startle, LES), an anxiety response sensitive to clinically effective anxiolytics (de Jongh et al., 2002). As shown in figure 1, exposure to bright light significantly reduced PPI, whereas subsequent return to the safe condition enhanced PPI (for details see figure legend). These changes were most marked at lower prepulse intensities (interaction effect of prepulse intensity*phase $F_{4, 80}=4.57$, $p<0.005$).

Schmajuk and co-workers also reported diminished PPI induced by dark-to-light transitions, an effect that was blocked by haloperidol (Schmajuk et al., 2009). However, in addition to PPI, the animals also showed attenuated startle, which indicates that the (lower) illumination conditions used in the Schmajuk study did not induce anxiety. Accordingly, the authors explained their findings by stating that sudden changes in environment illumination (i.e. novelty) may evoke dynamic changes in dopaminergic circuits that modulate the startle response and prepulse inhibition (Schmajuk et al., 2009).

In conclusion, the currently available studies, although limited, demonstrate that psychological stress can indeed affect PPI (table 1.b.). However, results are not unequivocal. Due to considerable variation in duration and time course of effect, it is unclear how long the PPI-disruptions will last, once the stressors are terminated, and further studies are

warranted to assess time-course and robustness and underlying mechanism involved in the observed alterations in gating mechanisms.

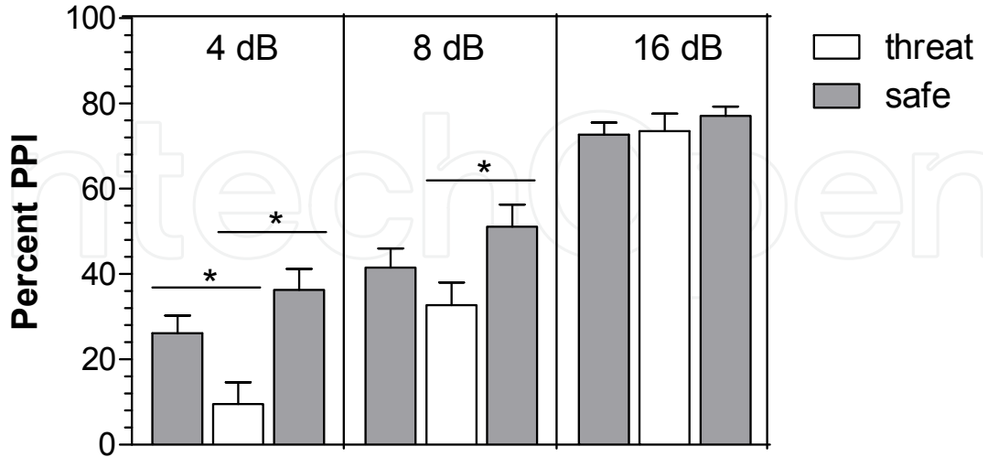

Fig. 1. PPI was measured under light-enhanced-startle conditions, with subsequent return to the dark (N=22). The test procedure was modified from de Jongh et al. (2002), and consisted of three phases. During phase 1 and 3 rats were tested in the dark, whereas during phase 2 the test cubicle was brightly lit (900 lux). Following a 5-min acclimatization period, each phase started and ended with five pulse alone trials. In between, five different trials were presented 10 times each: pulse alone (115 dB, 50 ms duration), pulse preceded by a 20 msec prepulse of either 74, 78 or 86 dB and no-stimulus trials, average inter trial interval 15 s. Shown is percent PPI (mean + S.E.M.) in safe (black bars) and threat (open bars) conditions. Potential threat (i.e. bright light) significantly reduced PPI, and subsequent return to the safe (i.e. dark) condition significantly enhanced PPI. * $P < 0.05$.

2.2 Effects of acute stress on sensorimotor gating: Human studies

In section 2.1. we have explored studies that investigated the influence of transient stress on the rodent PPI response. In the next sections, studies on human subjects are discussed, where stress has also been found to affect PPI. For instance, in a recent study, intravenous infusions of cortisol, in a dose resembling the physiological cortisol secretion in response to a moderate stressor, were shown to disrupt PPI in healthy participants (Richter et al., 2010). The disruptions reached a maximum at 20 minutes after administration, and returned to baseline another 20 minutes later. In an older study, Grillon and Davis investigated effects of stress and shock anticipation on PPI and startle in healthy subjects (Grillon & Davis, 1997). Basically, they measured PPI both when the subjects anticipated shocks (i.e. the threat condition) and when no shocks were anticipated (i.e. the safe condition). The authors argued that the fear induced by the threat condition would be superimposed on a generally stressful experience of the experiment. To distinguish effects of general alertness, they added a nonadversive control condition with a different group of participants. In this control experiment, participants were asked – and being paid for – to keep attention to auditory, visual and tactile stimuli in the test environment. As a result, both shock anticipation (i.e. fear) and attention to external stimuli significantly increased PPI. Regarding the increased PPI in the fear condition (later replicated by (Cornwell et al., 2008)), the authors suggested that threat of shock may have increased the general level of alertness,

which facilitates the processing of stimuli, thereby enhancing the effectiveness of the prepulse in inhibiting the startle response.
Repeated periods of shock anticipation however, were found to diminish PPI, an effect that was hypothesized to represent a progressive deficit in sensory functioning due to the prolonged stress of repeated shock anticipation. Apparently, this finding is not in agreement with animal work, where foot-shock stress had no effect on PPI (section 2.1.2). However, an important difference between human shock anticipation and the animal foot-shock paradigm is the physical component of the stress: during the entire experiment, human subjects only received a single shock, while animals were repeatedly exposed to shocks. In other words, the human threat-of-shock paradigm generally represented the psychological stress of potential threat, while the animal foot-shock stress had a large physical component of actual shocks, which might be less powerful. In this view, the human findings are consistent with the animal studies of (potential) threat, where diminished PPI was induced by the potential threat of bright light, and by the threat of predation (section 2.1.3.).

2.3 Effects of acute stress on sensory gating: Human studies

In addition to PPI, the brain's pre-attentive inhibitory functions are evaluated by an electrophysiological response-reduction paradigm, which is a paired-click test, wherein the P50 (or P1) wave of the vertex auditory event-related potential (i.e. computerized averages of the brain's electrical response to sound) is recorded. In healthy subjects, the P50 response to the second stimulus is generally attenuated (i.e. sensory gating), whereas in patients with schizophrenia and other psychiatric illnesses it is not suppressed (Adler et al., 1982; Adler et al., 1994), indexing deficits in filtering out irrelevant sensory stimuli (White & Yee, 1997). Like PPI, auditory sensory gating is influenced by stress. Note, that although the two experimental measures of brain inhibitory function are related, they are not identical in every respect, and partly regulated by different brain structures (Braff et al., 2001a). However, the fact that PPI and P50 gating are both measures of sensory gating that are influenced by stress, may point to possible common sources of functioning within the brain.
A few studies have reported decreased sensory gating following a stressful intervention. Effects of cold stress have been evaluated by the cold-pressor test, in which subjects have to submerge a hand to the wrist in cold water for a fixed period. To control for successful stress induction, subjective distress and arterial blood pressure were measured. With respect to PPI, the studies reported transient but significant deficits in response to cold stress, in addition to increased distress ratings and higher systolic arterial tension (Johnson & Adler, 1993; Ermutlu et al., 2005). Brief psychological stress has been found to exert similar effects. In a study by White and Yee (1997), subjects were administered an oral arithmetic task; this mentally stressful task resulted in reduced P50 suppression in the participants. Possible effects of attention were ruled out by adding an equally difficult, but non-stressful arithmetic task, which did not affect P50 suppression.

2.4 Conclusion section 2

In table 1.a. and 1.b., an overview is given of studies reporting on effects of acute stressors in adult life on measures of sensory gating. Available evidence, from both animal and human subjects, indicates that acute stress can modify sensory gating. However, underlying neurobiological mechanisms remain poorly understood. Possibly, in first instance, moderate

threat or attention to the environment could facilitate processing of sensory stimuli, for instance, via increased cortical arousal. Indeed, substantial evidence confirms that directing attention to the prepulse signal enhances PPI in humans and, likewise, emotional learning has been shown to enhance PPI in rats (reviewed by Li et al., 2009a). Severe or prolonged stressors on the contrary, may cause (progressive) loss of sensory perception that functions to reduce the impact of impending aversive events (Grillon & Davis, 1997). Particularly, these perceptual changes may be mediated by cortisol and CRF-induced activation of the mesolimbic dopamine system, a neural circuitry implicated in both stress responsivity and PPI.

However, some studies do not find an effect at all. From the animal work under review, this appeared to be most often the case when physical stressors were used, as opposed to psychological stressors (compare, table 1.a. and 1.b.). Due to the small number of available studies, it is difficult to draw definite conclusion from this finding. Clearly, the rodent PPI response is strain, age and gender dependent (Palmer et al., 2000; Swerdlow et al., 2006; Pietropaolo & Crusio, 2009), and stress appears to differentially influence PPI across strains and sexes (Varty & Geyer, 1998; Faraday et al., 1999). Despite these limitations, it could be speculated that psychological stressors may have a higher ethological validity, which could produce more pronounced effects on PPI. In this respect, it is interesting to note that the stress that is associated with episodes of relapse in schizophrenia patients is often of a psychological nature (Walker & Diforio, 1997). However, more studies on the effects of different types of stress on PPI are needed to reach a conclusion at this point.

Physical stress						
Subject	**Intervention**	**Stress-test interval**	**PPI**	**Startle**	**P50**	**Reference**
Human	Cold stress	0	n.d.	n.d.	↓	Ermutlu et al., 2005; Johnson & Adler, 1993
Rat	Cold stress	20 min	↓	=	n.d.	Leitner, 1986
Rat	Foot-shock	5 days	↑	↑	n.d.	Pijlman et al., 2003
Rat	Foot-shock	0, 24 and 48 hr, 9 d	=	=	n.d.	Bakshi et al., 2011
Rat	Foot-shock	2 weeks	=	=	n.d.	Bijlsma et al., 2009
Rat	Restraint	0	=	=	n.d.	Acri, 1994
Rat	Restraint	5 min	↓ , =	=	n.d.	Faraday, 2002
Rat	Restraint	30 min	↓	=	n.d.	Sutherland & Conti, 2011
Rat	Restraint	3 weeks	=	=	n.d.	Bijlsma et al., 2009

Table 1.a Overview of animal and human studies on effects of physical stressors in adult life on measures of sensory gating. PPI, prepulse inhibition; P50; P50 wave of event-related potential; n.d., not determined; ↑, ↓, =, response is improved, diminished, unchanged, respectively, when compared to control conditions.

Emotional stress						
Subject	**Intervention**	**Stress-test interval**	**PPI**	**Startle**	**P50**	**Reference**
Human	Mental stress	0	n.d.	n.d.		White & Yee, 1997
Human	Attention Threat - brief prolonged	0	↑ ↑ ↓	= ↑ n.d.	n.d.	Grillon & Davis, 1997
Rat	Threat (intense light)	0	↓	↑	n.d.	Current chapter
Rat	Predator	24 hrs	↓	=	n.d.	Bakshi et al., 2011
Rat	Predator	0, 46 hrs, 9 d	=	=	n.d.	Bakshi et al., 2011
Rat	Novelty (light)	0	↓	↓	n.d.	Schmajuk et al., 2009
Mouse	Social defeat	24 hrs	↓	=	n.d.	Brzozka et al., 2011
Rat	Witness stress	0	=	=	n.d.	Acri, 1994
Rat	Witness stress	5 days	=	=	n.d.	Pijlman et al., 2003

Table 1.b Overview of animal and human studies on effects of emotional stressors in adult life on measures of sensory gating. PPI, prepulse inhibition; P50; P50 wave of event-related potential; n.d., not determined; ↑, ↓, =, response is improved, diminished, unchanged, respectively, when compared to control conditions.

Based on the available studies, it is suggested that in healthy organisms, alterations in PPI induced by acute stress in adulthood are probably reversible, not causing permanent break down of gating mechanisms. Considering the neurodevelopmental theory of schizophrenia (section 1.3), it may be more etiologically relevant to apply the experimental stressors in early life. Therefore, in the next section, the effects of neurodevelopmental interventions on the rodent PPI response will be discussed.

3. Early-life stress and prepulse inhibition: neurodevelopmental animal models

According to neurodevelopmental theories (section 1.3), schizophrenia is considered a developmental disorder, influenced by both genes and the (early) environment. To get more insight into the possible role of early risk factors in the development of schizophrenia, early-stress paradigms are applied to laboratory rodents. In the following section, some common approaches for introducing developmental stress are reviewed, with their subsequent impact on PPI in later life. Note that this section does not attempt to exhaustively cover all available types of early stress in relevant animal models. The

interested reader is referred to more in-depth articles on this topic (Van den Buuse et al., 2003; Markham & Koenig, 2011).

3.1 Isolation rearing

One developmental manipulation that has received particular attention with respect to PPI is isolation-rearing. In this procedure, rats or mice are housed in single cages from the time of weaning (about 21 days after birth) until adulthood (Bakshi & Geyer, 1999; Varty et al., 1999; Varty et al., 2006; Pietropaolo et al., 2008), and thereby deprived of social contact with their peers during (neuro)development (Einon & Morgan, 1977). In comparison to group-housed controls, postweaning-isolated rodents exhibit a range of brain and behavioral changes, reminiscent to schizophrenia (Powell et al., 2003; Van den Buuse et al., 2003; Harte et al., 2007). Several studies have reported PPI deficits in isolation-reared rats (Geyer et al., 2001) and mice (Varty et al., 2006; Pietropaolo et al., 2008), which could be reversed by pretreatment with typical and atypical antipsychotics (Varty & Higgins, 1995). However, subsequent studies have indicated that the effect of isolation rearing is strain dependent (Weiss et al., 2000), sensitive to housing conditions (Weiss et al., 1999), developmental timing (Wilkinson et al., 1994), and could be prevented by handling the isolated rats (Krebs-Thomson et al., 2001). Moreover, in order to effectively disrupt PPI, isolation rearing has to be maintained until the moment of testing (Bakshi & Geyer, 1999; Varty et al., 1999). Based on these drawbacks, the validity of isolation rearing as possible animal model for early life effects on schizophrenia-related behaviors is considered questionable (Geyer et al., 2001; Varty et al., 1999).

3.2 Maternal separation

Since rats and mice are born at a more immature stage of development than humans, neonatal interventions in these animals are comparable with adverse events in mid-late gestation in humans (Van den Buuse et al., 2003). In this respect, maternal separation, being a neonatal neurodevelopmental model, differs fundamentally from isolation rearing (see previous section), which is a post weaning model. Maternal deprivation, or the temporary separation of rodent pups from their mother early in life, leads to various neurochemical changes, some with relevance to schizophrenia (Van den Buuse et al., 2003).

At the behavioral level, a single 24-hours period of maternal deprivation (at postnatal days 6 or 9) has been shown to induce deficits in PPI in a delayed fashion (i.e. arising after puberty), suggesting that certain long-term processes are set in motion by the early deprivation (Ellenbroek et al., 1998). These deficits could be reversed by pretreatment with typical and atypical antipsychotics (Ellenbroek et al., 1998). The fact that changes in PPI do not appear before adulthood, led Ellenbroek and co-workers to investigate whether the effect is unavoidable, or rather dependent on manipulations after the deprivation period (Ellenbroek & Cools, 2002). First, they combined maternal deprivation with the post weaning isolation rearing procedure (see section 3.1.). Surprisingly, whereas both procedures were found to reliably disrupt PPI when applied separately, together they had no effect. Furthermore, they investigated the role of the mother, as the deprivation procedure obviously affects the dam, as well as the pups. To do this, either half of the litters were maternally deprived (in this way, the mother had pups to nurse during the deprivation period), or maternally deprived mothers were cross fostered to non-deprived pups and vice versa. In all cases, the pups displayed small deficits in PPI, compared to fully deprived controls, suggesting that the behavior of the mother, and possibly, her milk

production, is also affected by the deprivation period. Thus, the authors concluded that the post-deprivation period is of crucial importance for the development of prepulse inhibition deficits in maternally deprived rats. Also, methodological factors such as timing, duration, and number of deprivation episodes, could possibly explain a lack of effect of maternal deprivation (Ellenbroek & Cools, 2002). Thereby, the ability of maternal separation to produce PPI-disrupting effects appears to be dependent on genetic strain (Ellenbroek & Cools, 2000), and species under study (rat vs. mouse) (Millstein & Holmes, 2007; Groenink et al., 2011; Naert et al., 2011).
Thus, maternal separation seems to induce PPI-deficits in a delayed fashion; however, the effect could be influenced by various protecting or facilitating post-deprivational factors, which might be similar to the influence of early-life stressors in humans.

3.3 Prenatal maternal immune activation

Epidemiological, clinical and preclinical studies have provided evidence that gestational exposure to certain infections, such as influenza, contributes to the etiology of schizophrenia (see Introduction). Similarly, animal models of maternal immune activation have yielded behavioral, neurochemical and neurophysiological findings that are consistent with observations in schizophrenia patients (Brown & Derkits, 2010). Currently, specific candidate infections have been identified that appear to be associated with an increased risk of schizophrenia, including rubella, influenza, herpes simplex, toxoplasma gondii, measles, polio, and genital and/or reproductive infections (Meyer & Feldon, 2009). A mechanism common to the immune response accompanying these infections, is the release of inflammatory cytokines. Consequently, elevation of maternal cytokine levels during pregnancy is thought to alter the trajectory of brain development, resulting in the induction of pathophysiological processes associated with mental illness (Markham & Koenig, 2011). Animal models of maternal immune challenge have used different immunogenic agents, all inducing a cytokine-associated inflammatory response in the mothers. However, other factors could be of relevance as well, for instance, immune activation is associated with fever, weight loss and elevated corticosteroids, which might compromise the offspring's *in utero* metabolic needs, thereby possibly affecting fetal brain development (Markham & Koenig, 2011). The effects of maternal infection on PPI have been investigated in several studies.
Systemic administration of bacterial endotoxin lipopolysaccharide (LPS) is capable of inducing a powerful immune response in the exposed animal, as well as fever and weight loss (Markham & Koenig, 2011). While LPS can be detected in both maternal and placental tissues, it is not found in the fetus (Ashdown et al., 2006), indicating that LPS itself is not responsible for the effects of maternal infection on the fetal brain. Several studies reported PPI disruptions in adult rat offspring of LPS infected mothers (Borrell et al., 2002; Fortier et al., 2007; Romero et al., 2007; Romero et al., 2010). These PPI deficits were associated with changes in dopaminergic transmission, and could be reversed by adult treatment with antipsychotics (Borrell et al., 2002; Romero et al., 2007). Interestingly, next to LPS, also turpentine, i.e. an inducer of local inflammation, at doses known to produce fever, significantly decreased PPI in adult offspring (Fortier et al., 2007). In analogy to the human situation, the influence of prenatal human influenza virus exposure on later brain development and behavior has been studied. Respiratory infection of pregnant BALB/c and C57BL/6 mice with the human influenza virus resulted in various behavioral abnormalities

in the adult offspring, among which deficits in PPI, which were sensitive for antipsychotics (Shi et al., 2003). In other studies, offspring of similarly infected mice displayed morphological and neurochemical changes reminiscent to schizophrenia, although the importance of these effects for the PPI deficits is unclear (Van den Buuse et al., 2003). Of note, however, is the large reduction in expression of the brain protein reelin in cortex en hippocampus (Fatemi et al., 1999), which is associated with both schizophrenia (Guidotti et al., 2000) and impaired PPI (Pappas et al., 2001). Lastly, viral infection is simulated in rats and mice by polyriboinosinic-polyribocytidilic acid (poly I:C), an agent structurally similar to double-stranded RNA, which forms the genetic material of some viruses. While administration of poly I:C to pregnant rodents can result in increased levels of cytokines in fetal brain, it only generates a non-specific immune response, without particular anti-viral antibodies (for references, see Markham & Koenig, 2011). With respect to PPI, treatment of pregnant mice or rats with poly I:C generates offspring that shows an impaired PPI response from post pubertal age (Ozawa et al., 2006; Li et al., 2009b; Piontkewitz et al., 2009; Vuillermot et al., 2010), which is presumably mediated by dopaminergic maldevelopment (Ozawa et al., 2006; Vuillermot et al., 2010).

Thus, animal models of prenatal maternal infection show altered fetal brain development and disrupted PPI in adult offspring, probably mediated by the maternal immune response. These findings are in line with epidemiologic and clinical investigations on infection as a risk factor of schizophrenia (Brown et al., 2010).

3.4 Multiple stressors

Based on the two-hit hypothesis of schizophrenia (see Introduction), several experimental animal studies have applied multiple interventions at different stages of development, to investigate their combined influence on schizophrenia-like behaviors. Possibly, this method may give additional mechanistic insights compared to single interventions alone. In the remaining part of this section, studies addressing the combined effects of multiple interventions on PPI will be discussed.

In one study, the interaction between stress and dopaminergic regulation of PPI was investigated (Choy & van den Buuse, 2008; Choy et al., 2009). After combining two subsequent stressors in neonatal and young-adult life (i.e., maternal deprivation and prolonged corticosterone treatment, respectively), PPI was tested in rats following acute injections with apomorphine. In controls and in rats that had undergone either one of the two stressors, the apomorphine treatment was found to disrupt PPI, while in the group that had experienced the multiple stress, no PPI-disruptions were observed in response to apomorphine (Choy & van den Buuse, 2008). According to the authors, their findings implicate an inhibitory interaction of early and late developmental stress, on dopaminergic regulation of PPI (Choy & van den Buuse, 2008). In a follow-up study, the authors suggested that this inhibitory interaction may be caused by receptor desensitization, because no changes were found in levels of dopamine D1 and D2 receptors (Choy et al., 2009). Notably, the finding that a subsequent stressor could reverse PPI-disruptive effects of a particular stressor, has been reported elsewhere (i.e., maternal separation and isolation rearing, (Ellenbroek & Cools, 2002). The above-mentioned experiments are in line with the idea that glucocorticoids could affect PPI by modulation of dopaminergic systems (see section 2.2.).

In most studies addressing the two-hit hypothesis, the first hit comprises a genetic predisposition. Consequently, it is investigated how genes interact with early stress to

produce schizophrenia-like neurochemical and behavioral alterations. As the focus of this chapter lies on the effects of stress on PPI, we will not discuss the neurochemical findings from genetic animal models of schizophrenia. Genotypes that have been found to interact with early stress to influence PPI include, nuclear receptor Nurr1 heterozygosity (i.e., 12 weeks of isolation rearing – Eells et al., 2006), Snap-25 mouse mutant *blind-drunk* (i.e., variable prenatal stress – Oliver & Davies, 2009), and NMDA receptor hypofunction mouse mutant (predation stress – Duncan et al., 2004). Notably, the latter study made use of predator olfactory cues (i.e., rat odor), which normalized the reduced PPI that was observed under control conditions in male mutants only. This result is in contrast to the study of Bakshi (section 2.1.3.), where predator exposure was found to decrease PPI in rats. However, an important methodological difference should be noted. Bakshi and co-workers actually introduced a predator in their experiment, while Duncan et al. only exposed the animals to predator odor. This difference in approach might have implications for the level of threat perceived by the subjects. In particular, when solely olfactory cues signal predation risk, perceiving animals may become more vigilant, which is thought to facilitate processing of sensory stimuli, possibly increasing PPI. Proximal presence of the predator, on the other hand, is likely to represent a severe stressor, which may induce disruptions in PPI due to progressive loss of sensory perception (see section 2.4.). Possibly, the delayed stress effect observed in the Bakshi study could be accounted for by recruitment of central mediators of the stress response, such as CRF.

In conclusion, although limited, the studies mentioned in this section suggest that combining multiple stressors, or a genetic vulnerability and stress, may induce stronger alterations in sensorimotor gating, when compared to one single intervention. Further relevant studies are warranted to test this hypothesis.

4. General conclusions

In this chapter, we have discussed studies that investigated the association between experience of stress and PPI, the latter being a highly validated model for schizophrenia; a mental disorder that is thought to be caused by an interaction of a constitutional vulnerability with environmental stress (see Introduction). From both animal and human studies, it is found that – by an unknown mechanism – application of acute stressors in adulthood is able to affect PPI, at least, transiently (table 1). Possibly, on the short term, moderate threat or attention to the environment could facilitate processing of sensory stimuli via elevated cortical arousal, leading to increased information processing; while severe or prolonged stressors may cause progressive loss of sensory perception that functions to reduce the impact of impending aversive events (section 2.4.). These perceptual deteriorations may be mediated by, for instance, cortisol- and CRF-induced activation of the mesolimbic dopamine system, a neural system that is implicated in both stress responsivity and PPI. Also, it is suggested that alterations in PPI induced by the acute stressors under study are probably reversible, not causing permanent changes to brain structures important in the regulation of PPI. These results are in line with clinical and epidemiological findings, which suggest that experience of stressful life events does not trigger onset of psychotic illness in healthy individuals (see Introduction). However, clearly, the acute and chronic stressors applied in the laboratory do not mimic 'naturally occurring' transient stress in the real world. This type of stress may come and go, and, depending on how long it stays, it

could ultimately cause permanent alterations in brain systems associated with psychosis in vulnerable individuals, as was observed in longitudinal studies (reviewed by Phillips et al., 2007; Walker et al., 2008).

The clinical observation that schizophrenia generally does not manifest until the third decade of life, suggests that it is the final outcome of pathological processes acting on the immature brain, and accordingly, it has led to formulation of the neurodevelopmental theory for the etiology of schizophrenia (see Introduction). In order to get more insight into the possible role of early environmental risk factors in illness development, early-stress paradigms are applied to rodents. Some developmental manipulations that have been shown to affect adult PPI include isolation rearing, maternal separation, and prenatal maternal immune activation (section 3). An alternative hypothesis within the framework of the neurodevelopmental theory of schizophrenia is referred to as the two-hit model. According to this model, early and late risk factors are not simply additive, but instead, the first hit will increase an individual's vulnerability for effects of a subsequent hit (see Introduction). Based on this theory, a few animal studies have applied multiple interventions at subsequent stages of development, to study their combined impact on schizophrenia-like behaviors, including PPI. Interestingly, although limited, results so far do not support the theory. Rather, instead of an augmentation, an inhibitory interaction of early and later developmental stress has been reported by two independent research groups. On the other hand, several studies have successfully identified candidate genes that could contribute to the induction of schizophrenia-like phenotypes in interaction with stress (section 3.4.). Possibly, investigating the interaction of these candidate genes with experimental stressors in animal studies, could represent a fruitful approach to model the link between stress and schizophrenia.

In humans, it is known that a wide variation exists in response to adversity, with some individuals being more stress-sensitive than others, and some individuals being more prone to developing an illness in response to environmental adversity than others (Kendler et al., 2005). Attempts have been made to explain the source of this variation; several studies have investigated the link between genetic polymorphisms and environmental stress in the etiology of schizophrenia. Some progress has been made, for instance, a recent genome-wide association study – contrasting large numbers of genetic variants in patients and controls – revealed significant associations between schizophrenia and polymorphisms in major histocompatibility complex (MHC), a region implicated in the bodily reactions to stress and infection (Stefansson et al., 2009). Also, although not yet replicated, the novel schizophrenia risk polymorphism ZNF804A was found to be associated with increased prefrontal-hippocampal and prefrontal-amygdala connectivity, possibly linking to increased sensitivity to stressful environments (Esslinger et al., 2009). In another study, the association between a serotonin transporter gene polymorphism (i.e. 5-HTTLPR), stress and disease characteristics was investigated in individuals diagnosed with psychotic disease (Goldberg et al., 2009). Therefore, symptoms occurring in the four-week period preceding hospitalization were evaluated in first-onset patients. As a result, stress (i.e. negative life-events preceding hospitalization) was found to be a predictor of depressive symptoms, but it did not interact with psychotic (or negative) symptoms. Together, the above-mentioned studies have genetically linked schizophrenia with several systems/brain structures important in stress regulation (e.g., MHC, amygdala, PFC). However, so far, no experimental studies have linked this gene-environment interaction with schizophrenia, which is probably caused by

the fact that schizophrenia is a complex disorder, putatively determined by the sum of numerous small effects of individual genes; hence the importance of using endophenotypes such as PPI in association studies.

In conclusion, the link between stress and PPI appears to be in line with neurodevelopmental theories of schizophrenia; a single stressor in adult life does not seem to cause lasting alterations in PPI, however, when applied during a critical stage of neurodevelopment or in genetically vulnerable organisms, stress could be more powerful in robustly affecting PPI. It is suggested, that future animal studies aimed at investigating the role of stress in the development of information processing dysfunctions in schizophrenia, may benefit from implementing human risk gene polymorphisms that are associated with stress (e.g. by making use of inducible transgenic mouse models).

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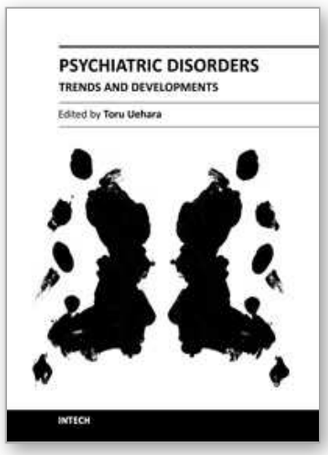

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Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, sever and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning 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.

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University Campus STeP Ri
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Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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