



Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia

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ABSTRACT

Cannabis use during adolescence increases the risk of developing psychotic disorders later in life. However, the neurobiological processes underlying this relationship are unknown. This review reports the results of a literature search comprising various neurobiological disciplines, ultimately converging into a model that might explain the neurobiology of cannabis-induced schizophrenia. The article briefly reviews current insights into brain development during adolescence. In particular, the role of the excitatory neurotransmitter glutamate in experience-dependent maturation of specific cortical circuitries is examined. The review also covers recent hypotheses regarding disturbances in strengthening and pruning of synaptic connections in the prefrontal cortex, and the link with latent psychotic disorders. In the present model, cannabis-induced schizophrenia is considered to be a distortion of normal late postnatal brain maturation. Distortion of glutamatergic transmission during critical periods may disturb prefrontal neurocircuitry in specific brain areas. Our model postulates that adolescent exposure to Δ^9 -tetrahydrocannabinol (THC), the primary psychoactive substance in cannabis, transiently disturbs physiological control of the endogenous cannabinoid system over glutamate and GABA release. As a result, THC may adversely affect adolescent experience-dependent maturation of neural circuitries within prefrontal cortical areas. Depending on dose, exact time window and duration of exposure, this may ultimately lead to the development of psychosis or schizophrenia. The proposed model provides testable hypotheses which can be addressed in future studies, including animal experiments, reanalysis of existing epidemiological data, and prospective epidemiological studies in which the role of the dose–time–effect relationship should be central.

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Abbreviations: 2-AG, 2-arachidonoylglycerol; AMPA, alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; Ca, calcium; CB, cannabinoid; COMT, catechol-O-methyl transferase; eCB, endocannabinoid; GABA, gamma-aminobutyric acid; LTD, long-term depression; LTP, long-term potentiation; Mg, magnesium; mGlu, metabotropic glutamate receptor; NMDA, N-methyl D-aspartate; NR2A, NR2A-subtypes of the NMDA receptor; NR2B, NR2B-subtypes of the NMDA receptor; PFC, prefrontal cortex; STDP, spike timing dependent plasticity; THC, delta 9-tetrahydrocannabinol.

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1. Introduction

There is now accumulating and converging evidence from epidemiological studies and reanalyses of existing data suggesting that cannabis use is a risk factor for the development of psychosis or schizophrenia (Smit et al., 2004; Semple et al., 2005; Moore et al., 2007). The risk increases with the frequency of cannabis use, indicating a causal relationship (van Os et al., 2002; Zammit et al., 2002; Arseneault et al., 2004; Smit et al., 2004; Henquet et al., 2004; Di Forti et al., 2009). In particular, the use of cannabis during adolescence increases the risk of development of schizophrenia later in life (Arseneault et al., 2002; Zammit et al., 2002; Henquet et al., 2004; Stefanis et al., 2004; Rubino and Parolaro, 2008; Konings et al., 2008).

The increased risk of developing schizophrenia is specifically due to the use of cannabis, since it is independent of the use of other drugs, e.g. alcohol (Arseneault et al., 2002; van Os et al., 2002; Zammit et al., 2002; Henquet et al., 2004). In addition, the outcome of psychosis or schizophrenia may be specific, because an association between cannabis use and later depression was not found (Arseneault et al., 2002), although more recent studies indicate a link between the use of cannabis and mood disorders such as bipolar disorder and depression (Moore et al., 2007; van Laar et al., 2007). However, this evidence is less strong than for the association between cannabis and schizophrenia, and might be due to overlapping symptoms between psychiatric disorders (Tsuang et al., 2004; Tamminga and Davis, 2007; van Os and Kapur, 2009).

Cannabis use preceding psychosis, the presence of a dose–effect relationship, and persisting association after controlling for potential confounding factors all suggest strongly that cannabis use plays a causal role in the onset of schizophrenia. However, in the determination of causal links, epidemiological research has its limitations. These studies, by their nature, cannot definitively prove that cannabis use is directly related to the risk of developing schizophrenia. Although they provide evidence of a causal link, the underlying neurobiological processes leading to an increased risk of psychosis have not been elucidated (Fergusson, 2004). To quantify the extent to which statistical linkages between cannabis and schizophrenia reflect underlying causal processes, a better understanding of the possible neurobiological pathways is needed.

To explain the neurobiology of cannabis-induced schizophrenia, the neurobiological literature was selectively reviewed using a toxicological approach (Niesink et al., 1995). This approach is based on the available epidemiological data, and implies a toxic substance affecting the central nervous system during a critical period, resulting in irreversible structural changes. These changes subsequently cause psychopathological effects. It is assumed that Δ^9 -tetrahydrocannabinol (Δ^9 -THC, henceforth mentioned as THC), the main psychoactive substance in cannabis, is the neurotoxic substance and that adolescence is the critical period. The interference of THC with a maturational process in the brain of adolescents is supposed to induce structural and functional changes. The following aspects will be reviewed in subsequent sections:

1. Is cannabis a neurotoxic substance?
2. Which brain structures are still undergoing maturation during adolescence?
3. Which of these structures are implicated in schizophrenia or psychosis?
4. Which physiological mechanisms form the basis for these maturational changes?
5. What is the role of the endogenous cannabinoid system in this process?
6. In what way does THC interfere with this physiological process?

One of the major problems in the debate revolving cannabis and schizophrenia is the definition of the term ‘schizophrenia’. In epidemiological studies, schizophrenia is used to describe a broad range of psychotic conditions. However, the psychiatric outcome of interest in the present review may be better described as a continuum between incidentally occurring psychotic symptoms and full-blown disorders as observed in patients diagnosed with schizophrenia seen in mental health clinics. Throughout this paper, the terms schizophrenia and psychosis are used as generic names, referring to this continuum. More detailed information on the nature and pathophysiology of schizophrenia is provided in Section 5.

Another issue is the different psychotogenic effects that cannabis can induce. High-dose intoxication with cannabis can result in acute psychosis, usually transient (Chopra and Smith, 1974; Thomas, 1996). Cannabis use has been associated with higher relapse rates and poor treatment outcome of schizophrenia-like disorders (Linszen et al., 1994; Buhler et al., 2002; van Os et al., 2002). However, this review focuses on the third effect of cannabis: the ability to induce a permanent psychotic disorder, usually with a time lag between exposure to cannabis and the onset of the disease.

From the results of the literature search, it can be postulated that THC adversely affects normal physiological maturational processes during adolescence. Usually, the interaction of endogenous cannabinoids with the CB1 receptor is critically involved in brain maturation through its regulating role in the release of glutamate. Through its action on CB1 receptors, THC can interfere with this normal physiological process, resulting in disturbed glutamate release, subtle neurotoxic effects and subsequent structural defects. Since maturation of the prefrontal cortex (PFC) is one of the most important processes during adolescence, THC may predominantly affect the maturation of specific neurocircuitries within this brain region. Moreover, dysfunctioning of the PFC is a key feature of schizophrenia (Callicott et al., 2003; Minzenberg et al., 2009). The working hypothesis is therefore that THC interferes with normal maturation of the adolescent PFC, ultimately giving rise to psychotic symptoms or schizophrenia.

2. Is THC a neurotoxic substance?

THC is the main psychoactive substance in cannabis (Gaoni and Mechoulam, 1964). The neurotoxicity of cannabis, i.e. THC, has

always been a subject of controversy. In vitro studies have demonstrated contradictory results. Some showed toxic effects of THC on cultured neurons, prevented by application of CB1 receptor antagonists (Chan et al., 1998; Campbell, 2001), whereas others demonstrated CB1-dependent neuroprotective effects of cannabinoids (Hampson et al., 1998; Shen and Thayer, 1998). Chronic exposure to THC in vivo may be toxic for hippocampal neurons, as suggested by decreases in the mean volume of neurons and their nuclei, synaptic density and dendritic length (Scallet et al., 1987) and a reduction in neuronal density (Landfield et al., 1988). However, indications for necrosis, edema, infection or trauma in adult rat brain tissue after THC exposure are lacking (Galve-Roperh et al., 2000). Administration of cannabis extracts to rodents causes long-lasting effects at the behavioral level (Carlini et al., 1970; Fehr et al., 1976; Stiglick and Kalant, 1982). However, chronic exposure of immature rats to THC induces more irreversible residual effects on behavior than chronic treatment of mature rats (Stiglick and Kalant, 1985), indicating that the age during exposure may be a critical determinant of neurotoxicity outcome (Scallet, 1991). This is confirmed by later animal studies demonstrating that chronic peripubertal, but not adult, cannabinoid exposure causes long-lasting alterations in memory and behavior, in particular in functions mediated by the PFC such as working memory and prepulse inhibition (Schneider and Koch, 2003, 2004; O'Shea et al., 2004). These results suggest that adolescent and adult THC exposure have differential effects on cannabinoid receptor functions. In rats, periadolescence appears to be a vulnerable period with respect to the adverse effects of cannabinoid treatment.

Human studies also suggest that adolescence may be a vulnerable period for producing long-term cognitive deficits. In general, studies on the long-term effects of cannabis on cognition only demonstrate evidence for some mild cognitive impairment, especially in learning and memory (Grant et al., 2003; Schweinsburg et al., 2008a). Functional imaging studies indicate altered brain response patterns among cannabis users despite similar task performance, suggesting increased neural effort and use of alternative strategies (Eldreth et al., 2004; Jager et al., 2006). However, both neuropsychological and functional imaging studies indicate that the detrimental effects of cannabis may be more pronounced when cannabis is used during adolescence (Jager and Ramsey, 2008; Schweinsburg et al., 2008a). Most imaging studies in adolescents have found alterations in working memory (Jacobsen et al., 2004, 2007; Schweinsburg et al., 2008b). Studies making a distinction between the initiation of cannabis use in adolescence and in adult life show attentional deficit and poor cognitive performance in early-onset cannabis users (onset before age 17), but not in late-onset users or control subjects (Ehrenreich et al., 1999; Pope, Jr. et al., 2003).

In summary, although the neurotoxicity of cannabis in general is not very convincing, more detailed studies suggest that cannabis could exert differential effects. Not only may adolescence be a vulnerable period for the adverse effects of cannabis, but cannabis may also affect particular functions that are regulated by the PFC. Finally, animal studies demonstrate that THC is responsible for these adverse effects.

3. Adolescence and brain maturation

Brain development is an organized and highly dynamic multistep process, which is genetically determined, epigenetically directed and environmentally influenced (Tau and Peterson, 2010). In contrast to earlier beliefs, this process continues both through childhood and adolescence, the developmental period during which the body and brain emerge from an immature state to adulthood (Spear, 2000; Steinberg and Morris, 2001). Although no precise borders can be defined, adolescence broadly covers the

stage between the non-reproductive (childhood) and reproductive stages (adulthood), i.e. in humans, an age range roughly starting between 10 and 12 years and finishing between 16 and 20 years (Spear, 2000). Adolescence is characterized by dramatic changes in brain growth and connectivity, and has been described as a critical period for the neurodevelopment of specific, mainly frontal cortical, brain regions (Slotkin, 2002; Chambers et al., 2003; Nelson, 2004; Cannon et al., 2005). Due to these excessive changes, adolescents are susceptible to developmental disturbances induced by exogenous substances (Rice and Barone Jr., 2000; Andersen, 2003; Smith, 2003; Spear, 2007).

Brain growth among infants and children is focused essentially on volume: as many brain cells as possible are created, with numerous connections to other brain cells. From childhood to adolescence, development shifts from producing a large number of neurons to creating efficient neuronal pathways. This efficiency is thought to be achieved by synaptic refinement, the process by which some connections between brain cells are pruned and eliminated, and "useful" neurons, synapses and dendrites are selected and preserved for the adult brain (Katz and Shatz, 1996; Cohen-Cory, 2002; Whitford et al., 2007; Purves et al., 2008; Luna, 2009). Presumably, this indicates that synapses that are most important to survival and optimal function flourish, whereas connections that are not being used vanish (Seeman, 1999; de Haan and Johnson, 2003; Luo and O'Leary, 2005).

3.1. Functional development

Adolescence is characterized by an increased need to regulate affect and behavior in accordance with long-term goals and consequences (Steinberg, 2005). Motivated behaviors that reflect the typical development of cognitive, affective, and social processes are changing to ultimately adult levels of performance (Ernst and Hardin, 2010). These changes in adolescent behavior come together with changes in the adolescents' physical and social environments, such as physical changes associated with puberty, changes in family and peer relationships and the increasing impact of society. Maturing adolescents show increasing capacity to attend selectively to information and to control their behavior (Adleman et al., 2002; Luna et al., 2004). The process of mental growth involves significant changes in behavioral response to cognitive, social and emotional stimuli, specifically related to increasing use of results of previous experiences (Knudsen, 2004). The maturation of complex cognitive processes are supported by development in specific core cognitive processes including the ability to plan, maintain information "online" (working memory), solve complex cognitive tasks, and exhibit self-regulation and inhibitory control (Luna and Sweeney, 2004). Working memory is fundamental to the performance of many cognitive tasks and day-to-day activities. Although working memory is already established in childhood, it matures over time and reaches adult performing levels in adolescence. Adolescents are able to perform more difficult working memory tasks than children (Luciana and Nelson, 1998; Demetriou et al., 2002; Davidson et al., 2006). Some aspects of working memory seem to mature early, whereas others have a more protracted maturation (Geier et al., 2009).

Recent studies focusing on the development of the social brain support evidence that adolescence also represents a period of significant social development (Blakemore, 2008). The social change includes heightened self-consciousness, increased importance and complexity of peer relationships, an improved understanding of others and a profound change in self-concept (Blakemore, 2008; Sebastian et al., 2008).

Adolescents report greater fluctuations in their emotional states and tend to experience highly emotional events more acutely (Larson et al., 2002). Emotional responses have not yet

consolidated and changes in emotional capacity are also seen during this developmental stage (Yurgelun-Todd, 2007).

3.2. Neuroanatomical development

During its development, the cerebral cortex experiences several transformations, including structural and neurochemical changes, which altogether result in a change in its functional capacities. Magnetic Resonance Imaging (MRI) studies showed that different areas of the cortex do not develop simultaneously: first cortical areas that serve relative simple tasks mature, before development of higher cortical domains is initiated. The development of higher domains among which specific areas within the PFC seems to be dependent upon the correct development of lower regions that takes place earlier in the process (de Haan and Johnson, 2003; Guillery, 2005). The PFC is considered one of the most functionally advanced areas of the association cortex (Fuster, 1999; Nelson et al., 2005), is mainly involved in higher order cognitive processing such as response selection, decision making and working memory (Krawczyk, 2002; Lee et al., 2007), and participates in the organization and planning of goal-directed tasks (Fuster, 1991; Goldman-Rakic, 1995). The sequence of cortical development is rostral-frontal and latero-medial (Gogtay et al., 2004). The association cortices that sub-serve executive functioning, attention and motor coordination comprise the last cortical regions to mature (Yurgelun-Todd, 2007), and some of the prefrontal regions may not be fully mature until young adulthood (Giedd et al., 1999; Toga et al., 2006; Gogtay et al., 2004). Although MRI studies do not have the resolution to visualize or measure changes at a synaptic level, combining the structural MRI data with post-mortem data, it has been speculated that the decrease in cortical gray mass, as measured by the MRI-studies, represents the fine tuning of neural connections via elimination of an excess of synaptic connections and dendrites and strengthening of relevant connections (Huttenlocher and Dabholkar, 1997; Selemon and Goldman-Rakic, 1999; Tau and Peterson, 2010).

Especially during the last decade efforts have been made to link the behavioral changes observed in adolescence with the maturation of specific regions in the brain. The orderly representation and control of information within mature neural circuitries are crucial for the appropriate processing of behavior. Abilities that rely on posterior brain regions appear to be stable by the age of 8 (Luciana and Nelson, 1998). Studies investigating the capacity of the PFC to regulate complex behavior suggest that adult levels of performance on more challenging tests of frontal lobe function are not reached until adolescence or early adulthood (Levin et al., 1991; Luciana & Nelson, 1998; Luciana, 2003). Abilities that involve interactions between posterior brain regions and the frontal lobe show an intermediate developmental pattern (Luciana, 2003).

Cognitive development through adolescence is associated with progressively greater efficiency of executive control capacities, and this efficiency is paralleled by increased activity within focal prefrontal regions (Rubia et al., 2000; Tamm et al., 2002). It seems that with increasing age prefrontal activity becomes more focal and specialized while irrelevant and diffuse activity in this region is reduced (Durstun et al., 2006; Tamm et al., 2002; Brown et al., 2005).

In the mature brain, working memory largely depends on an intact dorsolateral prefrontal cortex (DLPFC). Maturation of the neural circuits that support working memory processes is illustrated by a fuller and more consistent functioning of frontoparietal regions with increasing task difficulty between childhood and adolescence. This process is followed by the spatial refinement of these cortical regions between adolescence and adulthood (Scherf et al., 2006; Tau and Peterson, 2010).

The maturation of prefrontal networks also plays a critical role in the emotional behaviors displayed by adolescents. The

development of prefrontal modulation over emotional processing as measured by functional MRI studies using affective challenges continues to develop throughout adolescence into early adulthood. Neural circuits subserving attentional processes seem to mature ahead of those supporting socioemotional functioning (Yurgelun-Todd, 2007).

For information from the outside world, cortical areas subserving high-order behavior completely depend on subcortical connections. Animal studies, specifically studies in rodents, suggest unique anatomical and functional changes during adolescence. An intact innervation of the cortex from subcortical structures during this time period appears to be a prerequisite for the proper maturation of specific cortical areas. Thus, lesions in neurons connecting subcortical structures, such as the amygdala and hippocampus, with the prefrontal cortex before adolescence lead to specific structural and behavioral changes at the end of adolescence and in adulthood. Such lesions studies have been proposed as good animal models for neurodevelopmental psychopathological disorders, such as schizophrenia (Bouwmeester et al., 2002; Lipska, 2004; Tseng et al., 2009).

The maturation of the prefrontal cortex is protracted compared with associated subcortical regions. This developmental imbalance suggests that typical adolescent behavior such as emotional instability and increased risk-taking are the result of competition between enhanced activity in subcortical systems (e.g. amygdala and nucleus accumbens) and less-mature top-down prefrontal systems (Hare et al., 2008; Casey et al., 2008; Steinberg, 2010).

3.3. Development of neurotransmitter systems

Since optimal prefrontal functioning depends on the dopaminergic and GABA-ergic systems (Sawaguchi and Goldman-Rakic, 1991; Arnsten et al., 1994; Vijayraghavan et al., 2007; Rao et al., 2000; Constantinidis et al., 2002), functional development of the PFC also suggests alterations of these neurotransmitter systems during adolescence. Indeed, dopamine systems in the PFC undergo substantial reorganization during adolescence (Spear, 2000). Basal PFC dopamine concentrations peak in early adolescence and decline thereafter (Andersen et al., 1997), and refinements in dopamine innervation of prefrontal pyramidal neurons occur (Woo et al., 1997; Tseng and O'Donnell, 2007). In addition, both the density of dopamine afferents to the PFC (Rosenberg and Lewis, 1994; Lambe et al., 2000) and the activity of the dopamine eliminating enzyme catechol-O-methyl transferase (COMT) increase during adolescence (Tunbridge et al., 2007). On the other hand, dopamine synthesis and turnover in the subcortical projection areas of the PFC such as the striatum are lower at the beginning of adolescence than in early adulthood (Teicher et al., 1993; Andersen et al., 1997). This change in dopamine balance between the PFC and subcortical structures of the mesolimbic dopamine system is accompanied by, and probably the result of, significant pruning of axons projecting to the neocortex (Bourgeois et al., 1994; Woo et al., 1997).

The integrity of adult PFC functioning is dependent on a delicate interplay between inhibitory, GABA-ergic, and excitatory, mainly glutamatergic, neurons (Constantinidis et al., 2002; Lisman et al., 2008; Benes, 2010). During adolescence, the GABA-ergic system undergoes significant maturational changes. Using ultrastructural techniques, Cunningham and colleagues demonstrated that fibers from the basolateral amygdala continue to form contacts with GABA-ergic interneurons in the prefrontal cortex of rats throughout adolescence (Cunningham et al., 2002, 2008).

Lewis et al have intensively studied the development of GABA-ergic contacts with pyramidal cells in the DLPFC of monkeys (Akil and Lewis, 1992; Cruz et al., 2003, 2009). They found that different GABA-ergic inputs to pyramidal cells undergo distinct develop-

mental trajectories with different types of changes during the perinatal period and adolescence. These changes are in harmony with the protracted maturation of behaviors mediated by primate PFC circuitry (Cruz et al., 2009). A specific type of GABA-interneurons, the parvalbumin (PV) containing interneurons, is important for the regulation of working memory and information transmission between cortical areas (Salinas and Sejnowski, 2001; Bartos et al., 2007). Synaptic inhibition from PV-interneurons controls the firing rates of pyramidal neurons and participates in the development of executive functions associated with prefrontal brain regions (Goldman-Rakic, 1999; Markram et al., 2004). Adult levels of executive functioning emerge relatively late in the postnatal development of primates, throughout childhood and adolescence (Alexander and Goldman, 1978). In primates, the delay in achieving mature performance on executive function tasks correlates with the delayed maturation of PV-inhibitory circuits (Rao et al., 2000; Uhlhaas et al., 2009; Behrens and Sejnowski, 2009). In humans, the input to GABA-ergic interneurons in the PFC appears to decrease strongly from adolescence to adulthood (Lewis, 1997; Spear, 2000).

In summary, adolescence is an important era in brain development during which stimuli from the external environment are implicated in anatomical and functional changes of the brain. Working memory, a key cognitive function underlying other complex cognitive abilities, undergoes significant maturation during adolescence. This is in line with the functional and anatomical changes seen in the PFC during this age period. Apart from the structural changes, brain neurotransmitter systems, such as dopamine and GABA, undergo dramatic changes during adolescence. These alterations are implicated in changes in information processing of the PFC.

4. Experience, sensitive periods and mechanisms of cortical plasticity

Before various cortical areas have reached their mature structure, they pass through several developmental phases. Although differences exist between different cortical areas in the mechanisms underlying this process of cortical maturation, the individual maturational processes are basically the same. First, vast numbers of synapses and neurons are formed, followed by synaptic strengthening and elimination and pruning of redundant arbors. The forming of these more efficient microcircuitries within the functional areas of the cerebral cortex is the last step in the formation of a mature network.

4.1. Experience

External stimuli play an important role in brain maturation, making the brain unique to the specific individual (Rakic et al., 1994; Lichtman and Colman, 2000). The role of external stimuli has been intensively studied in brain development during early postnatal life (Quinlan et al., 1999; Zuo et al., 2005), but adolescent brain development has received little attention (Nelson, 2004). Experience is thought to play an important role in the strengthening and loss of synapses and dendritic and axonal arbors (Purves et al., 2008; Tau and Peterson, 2010). Through inducing patterns of neural activity, experience causes a cascade of events that refine the initially coarse connectivity into precise circuits. This has been clearly demonstrated for monosensory stimuli in the refinement of less evolved cortical regions such as the visual cortex (Quinlan et al., 1999; Berardi et al., 2003), olfactory cortex (Brunjes and Frazier, 1986; Zou et al., 2004; Franks and Isaacson, 2005), barrel cortex (Micheva and Beaulieu, 1997; Zuo et al., 2005) and auditory cortex (Reale et al., 1987; Kral et al., 2005), but has also been shown for more sophisticated functions, including bird song and language

development in humans (Buonomano and Merzenich, 1998; Doupe and Kuhl, 1999; Neville and Bavelier, 2002; Nordeen and Nordeen, 2004). There are several indications that the underlying mechanisms of experience-induced synaptic plasticity of sensorimotoric cortical areas may be generalized to other, more complex, cortical areas such as those in the PFC. Deprivation of complex stimuli in vulnerable periods, such as rearing in an impoverished environment (Benefiel et al., 2005) and social isolation (Hall, 1998), results in permanent disturbances in adult behavior, disturbances that seem to be mediated by defects in the neural circuitry within the PFC (Card et al., 2005). Deprivation studies also have shown that social play behavior, the first form of non-mother directed social behaviors displayed by most adolescent mammals, is essential for appropriate social, cognitive and sexual development (Vanderschuren et al., 1997).

4.2. Sensitive periods

Experience-dependent modifications typically occur during postnatal “sensitive periods” (Sur and Leamey, 2001; Knudsen, 2004). Sensitive periods are permissive temporal windows during which activity-dependent synaptic rearrangements occur, and after which mature connectivity is established. Critical periods are a special class of sensitive periods that result in irreversible changes in brain function (Knudsen, 2004). After a sensitive period, synaptic reorganization is more difficult to induce (Knudsen, 2004; Johnson, 2005; Fox et al., 2010). Sensitive periods start once the relevant neural pathways have developed. Critical or sensitive developmental periods have been well defined for a series of sensory and motor systems, but not for higher-order behavior. However, this does not mean that they do not exist. Although not experimentally demonstrated yet, it is plausible to assume that the maturation of higher-order neural circuits in adolescence occurs during sensitive periods (Tau and Peterson, 2010). Experience that occurs before the “opening” of a sensitive period will have no effect on the maturation of the circuit. Experience-dependent shaping of high-level circuits cannot occur until the computations being carried out by lower-level circuits have become reliable (Fig. 1). This implies that sensitive periods for regions of the brain that process high-level information cannot open until relevant information from lower level areas is sufficiently precise and reliable, and the reliable encoding of low-level information in turn depends on earlier sensitive critical period experience (Knudsen, 2004). Complex behaviors may comprise multiple sensitive periods. Thus, the development of complex functions involves cascades of sensitive periods affecting different levels of processing at different ages (Knudsen, 2004). Although stimuli from the cognitive, social and emotional domain are thought to be important for appropriate brain maturation during adolescence, it does not exclude an important role for this type of stimuli during critical or sensitive periods during infancy and childhood. For example, social contacts with parents has shown to be important for brain plasticity early in life (Helmeke et al., 2009; Musholt et al., 2009), whereas social contacts with peers are thought to be important for brain development during adolescence (Leussis and Andersen, 2008).

4.3. Brain plasticity

The remodeling of existing synapses has a key function in the reorganization and fine-tuning of neural circuits during sensitive periods (Citri and Malenka, 2008). Most of what we know about these activity-dependent changes in neural circuits at the synaptic level comes from electrophysiological studies of long-term potentiation (LTP) and long-term depression (LTD). During the time span of the sensitive period, synaptic connections are

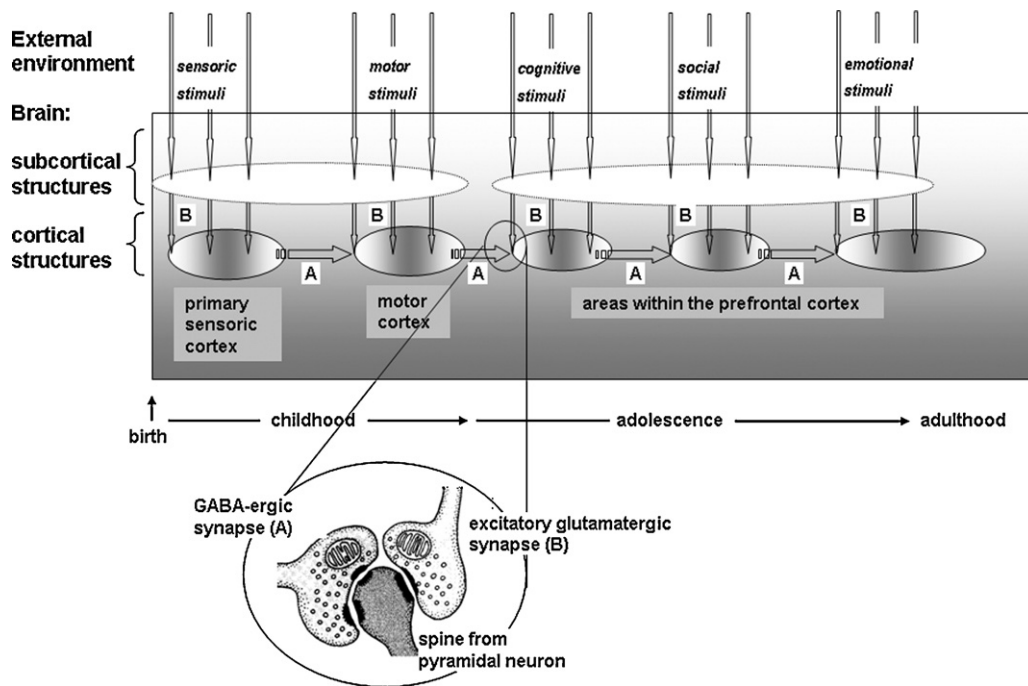


Fig. 1. Impact of environmental stimuli on adolescent brain maturation.

After birth external stimuli trigger, via subcortical structures, final maturation of specific cortical areas during critical and sensitive periods. Before birth, the development of specific cortical areas is mainly regulated by endogenous factors. After birth, regulation is performed by external stimuli. Shortly after birth, most of the stimuli are monosensory in nature, gradually followed by more complex stimuli, in combination with information that has already been stored (see text). Cortico-cortical connections regulate the onset of a specific critical period by depolarisation of postsynaptic membranes (A). Presynaptic stimulation by external stimuli ensure the release of glutamate (B). Simultaneous glutamate release and depolarisation of the postsynaptic membrane allows for activation of “immature” NMDA receptors and strengthening or pruning of the synaptic connection (see Fig. 2).

stimulated by neural activity in the form of electrical stimulation. The strength and pattern of activity at a given synapse produce transient or enduring potentiation or depression of communication between neurons (Martin et al., 2000; Morris, 2006; Purves et al., 2008). LTP and LTD require NMDA-receptor activation and the influx of Ca^{2+} -ions. Ca^{2+} -ions act as a second messenger which may modify the synapse structurally (Yashiro and Philpot, 2008). In case of LTP, this will strengthen the synaptic connection, in the case of LTD, this might lead to a weakening and ultimately pruning of the synaptic connection (Segal, 2005). The pruning of the synapse might in turn lead to retraction and ultimately removal of dendritic branches. Whether the initially established synapses are strengthened or removed depends on synchronization of the pre- and postsynaptic membrane; the postsynaptic membrane needs to respond to presynaptic neurotransmitter release (Herron et al., 1986; Segal, 2005; Yashiro and Philpot, 2008). Synchronization stabilizes the synapse, whereas failure to synchronize leaves the postsynaptic membrane unstable, leading to retraction and elimination of the synapse.

4.3.1. Silent synapses

Presynaptic stimulation might be a consequence of external stimuli. Via subcortical structures, external stimuli are transformed into action potentials inducing presynaptic neurotransmitter release in the cortex. Thus, external stimuli indirectly activate glutamatergic neurons which results in an efflux of glutamate and subsequently in an activation of NMDA-receptors.

Probably, at the start of the critical period, the early postsynaptic membranes contain an abundance of silent synapses that lack AMPA-receptors (Hanse et al., 2009). These synapses contain NMDA-receptors that are unresponsive to glutamate, due to blockade of the ion channels by Mg^{2+} . To allow ion influx, the blocked NMDA receptor pore needs to be

dislodged (Mayer et al., 1984; Isaac et al., 1997; Isaac, 2003). This only occurs when the postsynaptic membrane is sufficiently depolarized: postsynaptic depolarization dissociates the Mg^{2+} from its binding site within the ion channel. Simultaneous glutamate binding will result in a fully activated channel. Thus, in order to dislodge the Mg^{2+} and to activate the ion channel, a coincidence of presynaptic glutamate release and postsynaptic depolarization is needed (Fig. 2A).

How and what depolarizes the postsynaptic membrane is not yet fully understood. There is evidence that back-propagating action potentials provide the necessary postsynaptic depolarization. The back-propagating action potential is to be viewed as a dendritic signal that provides information to synapses about the firing state of the postsynaptic neuron (for review: Colbert, 2001). Because GABA-ergic neurotransmission plays an important role in the demarcation of the critical period (Hensch, 2005a,b), it is also possible that GABA-ergic neurotransmission plays a role in the depolarization of the postsynaptic membrane. In this context, the finding that during development inhibitory synapses transiently release glutamate might be of interest (Gillespie et al., 2005). It might be that GABA-ergic interneurons derived from already mature brain areas are responsible, which could explain the order in postnatal neocortical maturation. Whether LTP or LTD are initiated is dependent on the different rates of repetitive synaptic activity; induction of LTP requires high-frequency activity and LTD is induced by low-frequency activity. Another determinant of LTP synaptic plasticity is the temporal relationship between activity in the pre- and postsynaptic neuron. At a low frequency of synaptic activity LTD will occur if presynaptic activity is preceded by a postsynaptic action potential whereas LTP occurs if the postsynaptic action potential follows presynaptic activity, a phenomenon referred to as spike timing dependent plasticity (STDP) (for review: Caporale and Dan, 2008).

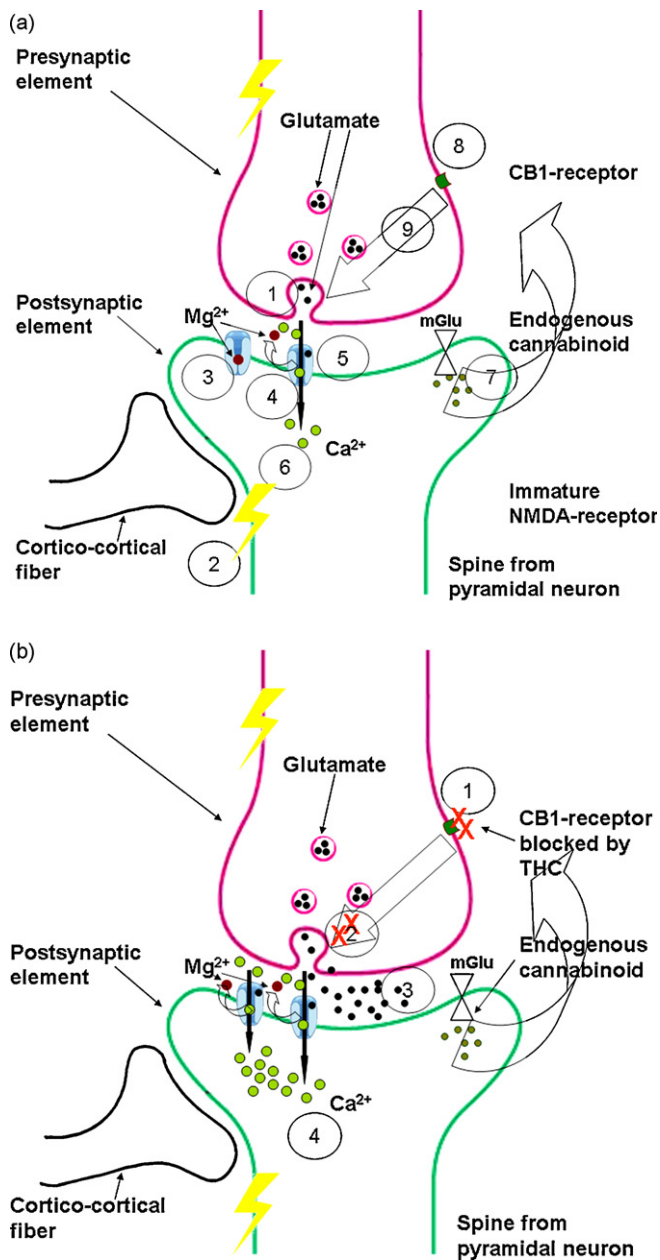


Fig. 2. Role of the endocannabinoid system in activity-regulated glutamate release and NMDA receptor changes.

(A) The process of strengthening and pruning is an activity-dependent process, in which the immature glutamatergic NMDA receptor plays an important role. With simultaneous presynaptic glutamate release (1), depolarisation of the postsynaptic membrane (2) lifts the Mg²⁺ blockade of the “immature” NMDA receptor (3 → 4), and binding of glutamate to the postsynaptic NMDA receptor (5) enables Ca²⁺ to cross the postsynaptic membrane through the immature NMDA receptor (6). The increased Ca²⁺ concentration starts the synaptic strengthening process. Activation of the metabotropic glutamate receptor (mGlu) stimulates the increase of postsynaptic endocannabinoid (eCB) synthesis, e.g. anandamide (7). Endogenous endocannabinoids control the release of presynaptic glutamate and GABA through an interaction with the presynaptic CB1 receptor (8 → 9). In this way, an excess of postsynaptic Ca²⁺ influx may be prevented.

(B) Transient blockade of the CB1 receptor, for example by exposure to exogenous cannabinoids such as THC (1), disrupts the protective effect of the endogenous cannabinoid system (2), thereby causing an excess of glutamate (3) and consequently too great an influx of Ca²⁺ (4) in the postsynaptic neuron. This causes a disturbance of the LTP/LTD balance, which may lead to pruning of the postsynaptic part of the synapse and possibly of the postsynaptic dendritic arbors. The ultimate result might be a disturbance in local neuronal circuitry (see Fig. 3).

4.3.2. The role of the postsynaptic calcium concentration

A coincidence of the postsynaptic depolarization and presynaptic glutamate release enables Ca²⁺ influx through the NMDA receptors. In the more enduring forms of plasticity, postsynaptic changes in intracellular Ca²⁺ regulate a variety of biochemical cascades, such as protein phosphorylation and changes in gene expression. This may greatly outlast the period of synaptic activity and can yield enduring changes in synaptic strength (Malenka, 1991; Zucker, 1999). The properties of STDP arise from timing-dependent differences in postsynaptic Ca²⁺ signals. If a postsynaptic action potential occurs after presynaptic activity, the resulting depolarization will relieve the Mg²⁺-block on NMDA receptors, which causes a relatively large amount of Ca²⁺ influx through the postsynaptic NMDA-receptor, resulting in LTP. When a postsynaptic action potential precedes a presynaptic action potential postsynaptic metabotropic glutamate receptors (mGlu's) are activated, resulting in the synthesis of endocannabinoids which acts as a retrograde messenger for glutamate release (see Section 6) and will reduce the amount of Ca²⁺ entry through the NMDA receptors, leading to LTD (Nevian and Sakmann, 2006). When presynaptic action potentials in STDP precede the postsynaptic action potential this results in a transient large influx of Ca²⁺ through the NMDA-receptor and a large increase in the postsynaptic Ca²⁺ concentration will occur, which is required for induction of LTP.

4.3.3. Changes in NMDA- and AMPA-receptors

The neural activity that the experience brings about is also responsible for the incorporation of AMPA receptors in the postsynaptic membrane. Binding of glutamate to the AMPA-receptors further depolarizes the postsynaptic membrane, which also unlocks the Mg²⁺ blockade of the NMDA receptor. Thus, incorporation of AMPA receptors changes the silent synapses into functional ones. Since more AMPA receptors are being incorporated during the course of the critical period, the functional NMDA receptor change is increasingly dependent on activation of AMPA receptors (Kerchner and Nicoll, 2008).

Further neuronal activity during the critical period changes the composition of the NMDA receptors (Ewald and Cline, 2009; Wang and Gao, 2009). NMDA receptors comprise both NR1 and NR2 subunits, which express distinct functional properties (Seeburg, 1993; Mori and Mishina, 1995). The NMDA receptor consists of four NR2 subunits and two types of NR2 subunits are discerned: NR2A and NR2B. The subunit composition of adult NMDA receptors is different from that of immature NMDA receptors. During the critical period, the ratio of NR2B/NR2A subunits changes. In the beginning, almost all subunits are of the glutamate sensitive NR2B type, and at the end of the critical period most of them are of the less sensitive NR2A type (Sinor et al., 2000; Kovacs et al., 2001). This NMDA receptor subunit change, together with the increase in less glutamate sensitive AMPA receptors, makes the postsynaptic membrane less effective in modifying synaptic efficacy through the critical period. Critical periods end once an individual has received adequate experience, and the relevant pathway is irreversibly committed to a particular pattern of connectivity.

The net result of the maturational processes during the critical period is a new local neuronal circuitry with functional characteristics that are different from the original circuitry. The NMDA receptor and the binding of glutamate are critically implicated in this refinement of cortical circuits. Blocking the binding of glutamate to the NMDA receptor with specific receptor antagonists during critical periods results in long-lasting defects in cortical circuits that might be reflected as functional disorders during adulthood (Johnston, 2004).

Although glutamate plays a central role in cortical maturation, overactivation of ionotropic glutamate receptors can induce either

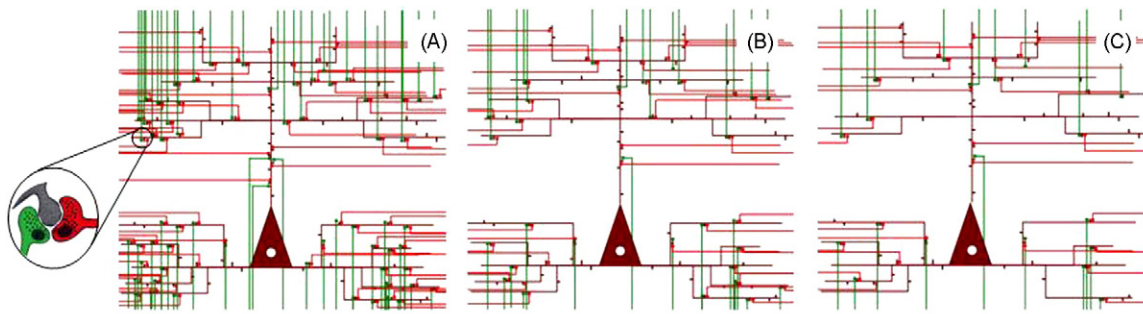


Fig. 3. Influence of cannabis exposure on neural circuitry development.

Subpart A represents normal cortical pyramidal neurons before pruning of synapses and neurites during a critical period. Subpart B represents the same pyramidal neuron as in subpart A, but now after a normal critical period during which several synapses, neurites and dendrites have been pruned, in this way forming part of a normal cortical circuitry. Subpart C represents the same pyramidal neuron as in subpart A, but now after a critical period during which too much glutamate has been released, e.g. due to exposure to exogenous cannabinoids. Such persistent circuitry alterations may result in disturbed neurotransmitter signalling in other brain areas ultimately leading to aberrant neural responses.

apoptosis or necrosis through excessive Ca^{2+} influx, a process known as excitotoxicity (Mody and MacDonald, 1995; Olney, 2003). This is illustrated by the fact that the immature brain is more sensitive to the excitotoxic effects of glutamate than the adult brain (Ikonomidou et al., 1999; Olney et al., 2000). Because the immature NMDA receptor is more sensitive to glutamate, the probability to induce such excessive concentrations of postsynaptic intracellular Ca^{2+} is increased during the critical period. Excitotoxicity may disturb the normal maturational processes by the formation of aberrant cortical connections (Olney, 2003). Thus, binding of glutamate to the NMDA receptor will have greater consequences during the critical period than outside this phase.

In summary, several areas in the prefrontal cortex undergo important changes during adolescence. It is not the number of cells that changes but the connections of several branches of different neurons. Changes within a certain area take place during a critical period. External stimuli are the trigger for these changes. Specific stimuli are important during critical or sensitive periods in specific areas. The external stimuli are supposedly responsible for the release of glutamate. Presynaptically released glutamate stimulates postsynaptic NMDA-receptors. Postsynaptic GABA-ergic connections probably depolarize the postsynaptic membrane, in this way unlocking immature NMDA-receptors. The depolarization of the postsynaptic membrane may also be caused by a process of backward propagated action potentials. Ca^{2+} -ions easily pass the ion channels within activated NMDA-receptors and enter the postsynaptic part of the synapse. Intracellular Ca^{2+} in combination with endogenous cannabinoids determine whether this will result in strengthening or pruning of the synaptic connection. Nature and number of these connections ultimately determine the quality of the mature neuronal network (Fig. 3).

5. Schizophrenia and the prefrontal cortex

Psychosis can occur in numerous organic and functional disorders of which schizophrenia is only one. Schizophrenia itself is a scientific construct to indicate a group of imperfectly understood brain disorders characterized by alterations in higher functions related to perception, cognition, communication, planning and motivation. The clinical symptoms are usually classified as positive, negative and cognitive symptoms (Carpenter, Jr. and Buchanan, 1994). Positive symptoms include hallucinations, delusions and lack of insight. Negative symptoms involve poverty of thought, anhedonia, apathy and a substantial reduction in social life and affective expression. Although positive symptoms are most prominent, cognitive impairments are considered to be the core feature of the illness (Elvevag and Goldberg, 2000; Gold, 2004).

Psychotic symptoms not only occur in schizophrenia and other psychiatric disorders. A significant proportion of the population has symptoms without a history of psychiatric or medical illness (van Os et al., 2000, 2009). Nowadays, there is much evidence for the existence of a continuum of psychotic experiences. The symptoms usually emerge in early adulthood.

The pathogenesis of schizophrenia is unknown. There is a substantial genetic component, and environmental experiences are involved. This is indicated by the familial incidence of schizophrenia: the risk for developing the disease increases with the degree of kinship (monozygotic twins have a concordance rate of more than 50%). Genetic research into schizophrenia suggests that multiple genes are involved in its etiology (McGuffin et al., 1994).

Several hypotheses have been advanced to explain the possible mechanisms giving rise to the widespread behavioral, neuroanatomical, neurophysiological, and neuropathological abnormalities of schizophrenia (for review: Keshavan et al., 2008). Most significant are the dopamine (imbalance) hypothesis and the neurodevelopmental hypothesis. The dopamine hypothesis states that altered dopamine function leads to the symptoms observed in schizophrenics: positive symptoms of schizophrenia are probably related to excessive dopamine activity in mesolimbic brain areas, and the negative/deficit syndrome is related to abnormally low dopamine activity in the PFC (Davis et al., 1991). The activity of mesolimbic dopamine terminals is under control of the PFC. Stimulation or inhibition of PFC function affects firing rates of subcortical dopamine neurons as well as dopamine release (Jackson et al., 2001; Murase et al., 1993). Dopamine, glutamate receptors and GABA-ergic interneurons regulate the activity of pyramidal cells in the PFC. This regulation includes the activation of GABA interneurons by glutamate. Recently, Bitanirwe et al. (2009) have shown that the glutamatergic neurotransmission on GABA-ergic neurons in the PFC is deficient in schizophrenic patients.

The neurodevelopmental hypothesis of schizophrenia proposes that schizophrenia is partly the result of an early brain insult affecting brain development, in which several factors such as infections, malnutrition or birth complications might play an etiological role (Weinberger, 1987). In particular, the lack of evidence of neurodegeneration or postmaturational neural injury supports a developmental hypothesis (Arnold, 1999). Therefore, most likely abnormal pruning or apoptosis of prefrontal synapses and fibers underlies schizophrenia (Feinberg, 1982; Keshavan et al., 1994; Glantz et al., 2006). Originally, the neurodevelopmental model was limited to the perinatal period. Recent findings that brain development continues well into adolescence indicate

that also adolescence can be regarded as a “vulnerable” period for neuronal network development. For proper development during childhood and adolescence, interaction with the environment, particularly the social environment, plays an important role. Therefore, social, emotional and cognitive stimuli might be involved in the maturation of mature neuronal networks, as indicated by additional risk factors for developing schizophrenia. Early parental loss either from death or separation, lower socioeconomic class, possibly as a result of increased stress or poor nutrition, and other socioenvironmental variables such as growing up in urban areas and migrational status have shown to be additional risk factors for developing schizophrenia (Allardyce and Boydell, 2006; Cantor-Graae, 2007; For reviews: Picchioni and Murray, 2007; Tandon et al., 2008).

Another important risk-factor for developing schizophrenia or closely related psychotic disorders is the use of cannabis during adolescence. At least nine independent studies support the finding that the use of cannabis can lead to an increased risk of psychosis later in life (Andreasson et al., 1988; Arseneault et al., 2002; Fergusson et al., 2003; Henquet et al., 2004; Mauri et al., 2006; Stefanis et al., 2004; van Os et al., 2002; Weiser et al., 2002; Zammit et al., 2002). A systematic review by Moore et al shows that risk of psychosis increases by about 40% in people who have previously used cannabis (Moore et al., 2007). This review also showed a dose–response effect: an increased risk of 50–200% in the most frequent users (Smye, 2008). One of the epidemiological studies (Arseneault et al., 2002), showed that children and adolescents who had used cannabis by the age of 15 years were 4.5 times more likely to have been diagnosed with schizophreniform psychosis at the age of 26 years; those who had used the drug by the age of 18 years were 1.6 times as likely to receive that diagnosis (Arseneault et al., 2002; Murray et al., 2008).

Psychotic symptoms are not fully expressed until brain development and maturation are largely completed, which is not until the end of adolescence. An additional indication for the necessity of a mature brain for the expression of positive symptoms is that both the NMDA-antagonists phencyclidine (PCP) and ketamine induce psychotic symptoms (Javitt and Zukin, 1991; Krystal et al., 1994) and neurocognitive disturbances similar to those of schizophrenia in adults, but not in young adolescents or children (White et al., 1982; Reich and Silvay, 1989; Baldrige and Bessen, 1990).

The limitations of the dopamine and neurodevelopmental hypotheses are significant. The dopamine hypothesis and the neurodevelopmental hypothesis are not mutually exclusive, and there have been various attempts to link them. It is currently believed that disturbed neuronal development leads to the development of instability in the networks involved in the regulation of dopaminergic activity between and within the PFC and subcortical mesolimbic structures (Feinberg, 1982; Keshavan et al., 1994; Glantz et al., 2006; Benes, 2010).

An excess of cognitive impairments has been found in samples of schizophrenic patients compared to controls (Bowie and Harvey, 2005). The cognitive impairments in schizophrenic patients are at least partly attributed to a dysfunctional working memory and thus to disturbances in the functioning of the PFC (Goldman-Rakic, 1999; Levy and Goldman-Rakic, 2000). This might be due to abnormalities in GABA-mediated neurotransmission (Hashimoto et al., 2008; Lewis et al., 2008; Mellios et al., 2009), regulating neuronal activity of glutamatergic pyramidal cells during working memory.

Nowadays, it is commonly believed that the biological basis of schizophrenia might be understood in terms of an abnormality in brain development. Several studies investigating the etiology of schizophrenia point to subtle changes of GABA- and glutamatergic networks within the prefrontal cortex (Benes et al., 1992; Reynolds and Beasley, 2001; Lewis et al., 2004; Benes, 2010). Genetic

approaches have identified several possible risk factor genes, some of which are related to mechanisms known to be important in the development of brain circuits and synapses (Harrison and Owen, 2003). Risk factors for schizophrenia suggest that the disrupted development is the result of an interaction between genetic and environmental factors. The disrupted neurocircuitry may upset the dopamine balance between cortical and subcortical structures, ultimately resulting in psychotic symptoms.

6. The cannabinoid system and cortical maturation

To prevent excitotoxicity induced by an extreme influx of Ca^{2+} through postsynaptic ion channels, the synapse controls the amount of glutamate that is presynaptically released. An important mechanism to regulate glutamate homeostasis is the endogenous cannabinoid system (Schlicker and Kathmann, 2001; Wilson and Nicoll, 2002; Chevalyere et al., 2006). It consists of cannabinoid receptors and endocannabinoid ligands that work on these receptors. At least two cannabinoid (CB) receptors have been characterized: CB1 and CB2 (Matsuda et al., 1990; Munro et al., 1993). The CB1 receptor is the most abundant G-protein-coupled receptor in the mammalian brain and is expressed at high levels in the basal ganglia, cerebellum, hippocampus and cortex (Herkenham et al., 1991; Glass et al., 1997). Most of the CNS effects of cannabinoid drugs are mediated by the CB1 receptor (Huestis et al., 2001, 2007). The CB2 receptor is mainly detected in the periphery (Munro et al., 1993). The identification of cannabinoid receptors resulted in the discovery of endogenous cannabinoid ligands, the two most important being anandamide and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Sugiura et al., 1995; Stella et al., 1997).

The endocannabinoids are not stored as classical neurotransmitters, but are released from the postsynaptic neuron and diffuse retrogradely across the synaptic cleft to stimulate CB1 receptors on the presynaptic neuron. Activation of these CB1 receptors transiently decreases neurotransmitter release from presynaptic terminals (Schlicker and Kathmann, 2001; Wilson and Nicoll, 2002; Chevalyere et al., 2006). This retrograde inhibition of synaptic transmission has been described for GABA-ergic and glutamatergic synapses throughout the whole brain, including the neocortex, suggesting that endocannabinoids represent a widespread mechanism of synaptic regulation (Schlicker and Kathmann, 2001; Wilson and Nicoll, 2002; Chevalyere et al., 2006). Furthermore, the endocannabinoid signaling acts on-demand and in a synapse-specific manner: endocannabinoids are released when they are needed (Marsicano et al., 2003) and only affect neurotransmitter release from their accompanying presynaptic site (Brown et al., 2003). All these qualities make the endocannabinoid system pre-eminently suitable as a physiological protective mechanism against excessive stimulation of glutamate receptors, which might easily appear during critical periods.

Exogenous cannabinoids affect the function of the endocannabinoid system. The regulatory role of the endogenous cannabinoid system in GABA and glutamate neurotransmitter release is disrupted by both synthetic cannabinoids (Kreitzer and Regehr, 2001; Yoshida et al., 2002; Chevalyere and Castillo, 2003) and THC (Mato et al., 2004; Hoffman et al., 2007). Possible mechanisms responsible for this disruption include down regulation (loss of binding sites) and desensitization (uncoupling from G-proteins) of CB1 receptors. These mechanisms have consistently been shown after chronic administration of both synthetic cannabinoid agonists and THC (Breivogel et al., 1999; Sim-Selley and Martin, 2002; Martin, 2005). By preventing endocannabinoid-mediated control over the homeostasis of glutamate and GABA, exogenous cannabinoids might dramatically affect the process of maturational refinement of cortical neuronal networks.

The endogenous cannabinoid system has a significant role in neural development. Both functionally active cannabinoid receptors and endogenous cannabinoids emerge early in the developing brain (Fernandez-Ruiz et al., 2004), being critically involved in the transition from synaptogenesis to synaptic communication in developing neuronal circuits (Harkany et al., 2008). In addition, CB1 receptors regulate the precise topography of the cortical whisker barrel map, suggesting a role in cortical network development (Deshmukh et al., 2007). However, research on the involvement of the endocannabinoid system in adolescent brain development is just in its infancy. Interestingly, the few studies available indicate a strong correlation between the presence of the CB1 receptor in a certain cortical area and its specific critical period (Mizoguchi et al., 2006; Deshmukh et al., 2007).

In the present review, we emphasize on the role of the endogenous cannabinoid system in strengthening and elimination of excitatory synaptic connections in cortical neurocircuitries during adolescence. This is because structural MRI-studies have shown that the maturation of specific cortical areas during adolescence is accompanied with thinning of the gray matter (e.g. Gogtay et al., 2004). It is generally believed that this change in gray matter is a consequence of pruning of synaptic connections (Giedd et al., 1999; Gogtay et al., 2004). Most of the synaptic attrition is achieved through the selective elimination of asymmetric junctions, on dendritic spines (Bourgeois et al., 1994; Luciana, 2003). Asymmetric synaptic contacts regulate excitatory, mainly glutamatergic, transmission. However, this does not imply that this “protective” role of endogenous cannabinoids during adolescent maturation is the only one. The eCB system has also an important role in the development of the neural system much earlier in life (Berghuis et al., 2007), which also makes the prenatal period a sensitive period for exposure to cannabis (Galve-Roperh et al., 2009; Schneider, 2009). In addition the eCB system plays an important role in cellular processes underlying learning and memory (Heifets and Castillo, 2009). However, these effects of cannabinoids are beyond the scope of this review.

In summary, activation of cannabinoid receptors on synaptic terminals results in regulation of ion channels, neurotransmitter release and synaptic plasticity. Neuromodulation of synapses by endocannabinoids is proving to have a wide range of functional effects, and they have been implicated in brain plasticity and learning and memory processes, which is beyond the scope of this review (for reviews: Harkany et al., 2007; Trezza et al., 2008; Heifets and Castillo, 2009; Fisar, 2009). Endocannabinoids are in a strategic position to regulate synaptic GABA and glutamate release in an on-demand feedback mechanism. Therefore, the endocannabinoid system seems to be critically involved in the regulation of neuronal refinement. Exogenous cannabinoids, including THC, can disrupt the regulatory role of the endocannabinoid system and thus can affect the process of maturational refinement of cortical neuronal networks.

7. General discussion

Using a toxicological approach and based on recent biological and medical literature, it is postulated that the exposure of cannabis,

more precisely THC, during adolescence results in disturbance of the experience-driven refinement of specific local neural circuits within the PFC. The dose, the exact time-window and duration of the exposure determine the severity and precise location of the cortical disturbance. The CB1 receptor is the primary target for this neurotoxic effect of THC. Under physiological conditions, the interaction of endogenous cannabinoids with the CB1 receptor is important in controlling the release of glutamate and GABA. Glutamate plays a prominent role in the process of strengthening and pruning of synapses during critical periods in postnatal development during which mature neural circuitries are established. A consequence of a transient disturbance of the cannabinoid control system by the exposure of THC is disruption in the release of glutamate, which might result in an anomaly of synaptic connections. The improper construction of local neural circuitries within the PFC has functional implications for physiological communication with other cortical and subcortical structures, mainly through transmission abnormalities of dopamine and GABA. Abnormal functioning of the PFC and disturbances in dopamine homeostasis are key elements in schizophrenia. Our model of the neurobiology of cannabis-induced schizophrenia is summarized in Table 1.

The core of our neurobiological model about the relationship between the use of cannabis and the development of schizophrenia is the interaction of the primary psychoactive ingredient in cannabis, THC, with its primary biological target, the CB1 receptor. After all, it is this specific interaction that subsequently induces a permanent structural effect that distinguishes cannabis use from other risk factors for schizophrenia. Although a few neurobiological models have already been proposed, little attention has been paid to the role of the CB1 receptor, the specific time-span of the exposure, and the permanent character of the lesion. These issues form the basis of our model. Although this model is based on available neurobiological evidence, it should be noted that several assumptions are made that require further elucidation.

First of all, cannabis contains more than 60 different cannabinoids, while in the current model it is assumed that THC is the toxic component. This is based on the fact that THC is the main psychoactive component in cannabis, and that it is also the main ligand for the CB1 receptor. The lasting effects due to exposure to cannabis as demonstrated in animal testing are a result of an interaction with the CB1 receptor. Further, it is assumed that postnatal developmental refinement of specific areas within the PFC takes place in a way homologous to that in other cortical areas that have been studied more extensively. Investigating experience-driven plasticity of specific PFC areas is difficult, among others because of the lack of information on specific stimuli necessary for this refinement. However, there are several indications that the underlying mechanisms of experience-induced synaptic plasticity of sensory cortical areas may be generalized to other, more complex, cortical areas such as those in the PFC. Thus deprivation of complex stimuli in vulnerable periods, e.g. rearing in an impoverished environment, play deprivation and social isolation, results in permanent disturbances in adult behavior, disturbances that seem to be mediated by defects in neural circuits within the PFC. However, until now there is no real proof that the same neurobiological substrates are implicated.

Table 1

Model of cannabis-induced schizophrenia: from etiology to symptoms.

Etiology: cannabis hampers the protective action of the endogenous cannabinoid system during a vulnerable period: adolescence.

Pathogenesis: lack of a protective system during sensitive periods of brain maturation of specific areas within the prefrontal cortex causes a disturbed neurotransmitter release (glutamate/GABA), affecting the strengthening and pruning process of synapses and dendrites.

Pathology: misshapen local cortical neurocircuitries within the prefrontal cortex due to mistakenly connected or lacking neural connections.

Pathophysiology: disturbed control (excitation and inhibition) of cortical and subcortical neural networks by the affected circuitries in the prefrontal cortex.

Symptoms: disturbed neurotransmission in the projection areas of the affected prefrontal cortical areas, e.g. overactive dopamine in the striatum, or hypoactive dopamine in the prefrontal cortex.

By analogy with the visual cortex, it might be expected that transformation of the immature NMDA receptor into its mature form, together with the incorporation of AMPA receptors in the postsynaptic membrane, is one of the mechanisms responsible for synaptic strengthening and pruning during the critical or sensitive period for specific areas within the PFC. Indeed, studies showing a decrease in efficacy (Burgard and Hablitz, 1993) and a transient change in concentration (Insel et al., 1990; McDonald and Johnston, 1990) of cortical NMDA receptors during development indicate that glutamate-NMDA receptor interactions are implicated in activity-dependent changes in cortical areas within the frontal lobe. Furthermore, in non-human primates, the number of excitatory synapses in the PFC declines substantially during adolescence until stable adult levels are achieved (Bourgeois et al., 1994). However, other mechanisms than the unique NMDA receptor subunit composition may also be involved in critical period synaptic pruning. Because the endocannabinoid system also regulates the release of GABA, temporary dysregulation of the CB1 receptor on GABA-ergic synapses through cannabis exposure may also have detrimental effects on the refinement of neural circuits within the PFC. It is not yet clear to what extent glutamatergic excitatory NMDA receptors and GABA-ergic neurons mutually interact during critical periods. Probably GABA-ergic neurons determine the onset of the critical period, whilst the NMDA receptor is involved in the functional change, i.e. the strengthening or pruning, of the synapse itself. This supports the view that higher brain structures developing during critical periods require both input from areas that have already undergone a maturational change and information derived from the external environment. In the present model, the first may be supplied by cortico-cortical connections, whereas the latter is provided by specific subcortico-cortical input. At the circuitry level, this would mean optimization of the connections between subcortical and cortical areas through elimination of redundant fibers and strengthening of the remaining ones. As a result, the described model predicts cortical structural abnormalities after cannabis exposure. However, these structural changes, such as an altered branching pattern of dendrites or changes in the number of synapses on cortical pyramidal cells, will be subtle and thus difficult to demonstrate. Current techniques are not able to determine such subtle structural changes in microcircuitries *in vivo*.

To study experience-driven changes in neural circuitries we mainly rely on animal data, certainly when focusing on the cellular, synaptic and dendritic level. The functional development of especially the prefrontal cortex in humans is more sophisticated than in non-human primates and other animals, which will have its reflection in the underlying neural construction. In animal studies it is therefore difficult to study disruptions of these higher order functions. Some of the striking symptoms in schizophrenia such as hallucinations and delusions seem to be restricted to humans; it is surmised that these phenomena do not occur in non-human primates or in other animals. For complex human illnesses, such as schizophrenia, etiological validity is difficult to assess in animal models, because little is known about the etiology of the illness. However, animal models can be used to test hypotheses about the possible etiology of the illness and studies in experimental animals can provide potentially important new insight into a range of brain mechanisms with relevance to schizophrenia (van den Buuse et al., 2005). And therefore, animal 'models' are an important tool in studying the symptoms and development of cannabis-induced schizophrenia, alongside approaches such as post-mortem studies, psychophysiological studies, imaging and epidemiology.

In the proposed model, a prominent role in the maturation of cortical areas is reserved for the endogenous cannabinoid system. Despite a suggested involvement for this system in neural

development, research on the role of the endocannabinoid system in adolescent brain development is just in its infancy. A comprehensive neuroanatomical analysis of CB1 receptors and endogenous cannabinoids during specific critical periods within particular areas of the frontal cortex is currently lacking. In addition, studies investigating the role of the endogenous cannabinoid system in strengthening and pruning of synapses during critical time periods in humans are needed. The few data currently available converge in the direction of a correlation between the presence of the CB1 receptor in a certain cortical area and its specific critical period (Eggen et al., 2009).

Because cannabis may induce several effects, the exact contribution of cannabis to the development of schizophrenia is difficult to determine. Cannabis has an acute effect, an effect on the long term and a precipitating effect in people with a pre-existing pathology. To study the mechanisms of cannabis-induced schizophrenia, it is necessary to separate these different effects. Therefore, in the real life situation the associations that are measured in epidemiological studies are the consequence of more than one effect of cannabis: a detrimental effect of cannabis on the construction of the maturing central nervous system and a provoking effect of psychoses in an already affected neural circuitry. With epidemiological studies it is not possible to discern these effects. The different effects of cannabis are most likely mediated by the same CB1 receptor, but the mechanisms of the pathological and physiological consequences of the cannabis-CB1 receptor interactions are different. In real life situations, these various effects of cannabis may occur simultaneously and will also mutually interfere with each other.

Although cannabis use is an important risk factor for the development of schizophrenia, it is only one of many. Other risk factors, such as birth complications or malnutrition during pregnancy, may provoke earlier or other brain lesions. Theoretically, there are several possibilities concerning the etiology of cannabis-induced schizophrenia. For example, the development of schizophrenia could be the result of an early lesion in combination with a challenge by the acute effect of cannabis in adolescence, an early lesion followed by a second lesion caused by the cannabis exposure in adolescence (two-hit model), or a permanent lesion produced by cannabis use during adolescence. In the first and the second model, cannabis is just a trigger for an already affected neuronal circuitry. However, animal (Stiglick and Kalant, 1985; Schneider and Koch, 2003; O'Shea et al., 2004) and human data (Arseneault et al., 2004) suggest that cannabis exposure alone may be a sufficient factor to induce a developmental brain defect that might result in schizophrenia. Neither of the first two hypotheses can explain these results.

Moreover, epidemiological studies until now have never shown that cannabis-induced schizophrenia would not occur in non-sensitive people. The research that has been done in vulnerable people concerns studies in people diagnosed with subclinical symptoms (Henquet et al., 2004). In fact, these people already suffered from a subclinical prodromal syndrome at the time that the exposure to cannabis took place. Therefore, there is a need for studies investigating a relationship of heredity for schizophrenia and additional risk posed by the use of cannabis.

It has been reported that a functional polymorphism in the COMT gene moderated the influence of cannabis use in adolescence on the development of psychosis in adult life (Caspi et al., 2005; Henquet et al., 2006). However, a disruption of the dopamine metabolism, for example by an inherited disorder of the COMT enzyme, seems rather an additional than a causal risk factor. A disturbed dopamine metabolism probably has a higher impact in case of an already disturbed dopamine regulation, e.g. as a result of structural changes. A disturbance of the dopamine metabolism alone is probably not sufficient to cause schizophrenia and

therefore it seems that a disruption of COMT, the metabolizing enzyme of dopamine, is not an implicit factor for the cannabis-induced schizophrenia. Although it cannot be excluded that a genetically disturbed regulation of dopamine metabolism may lower the threshold for symptoms revealed by cannabis-induced structural deficits.

Although the present model certainly does not exclude other risk factors, it should be kept in mind that in this model, a dose–time–effect relationship is responsible for the toxic effect of cannabis during late postnatal development. This is possibly also one of the main reasons why not everyone who used cannabis during adolescence will develop a permanent psychosis. Lower exposure will result in a less serious, probably sub-threshold effect. On the other hand, the model is useful to explain how in individual cases people that are not vulnerable for schizophrenia might develop psychosis in adult life after cannabis exposure during adolescence.

Cannabis alters perception and has amnesic effects, therefore theoretically, it is possible that the effects of cannabis assert themselves already much earlier in the chain of events underlying experience-dependent maturation (Fig. 1). As described above, the “experience” necessary for brain maturation in adolescence is probably formed by an unknown combination of cognitive, social and emotional stimuli. Deprivation of such incentives at the beginning of the chain would ultimately yield into the same effects as a blockade of neurobiological mechanisms further down the chain. It is well known that acute cannabis intoxication has an inhibitory effect on social and emotional behavior and on cognitive functioning. Acute intoxication by cannabis might therefore be similar to a deprivation of these stimuli. This might suggest that cannabis itself has no effect on the neurobiological processes in this developmental chain of events, but hampers the start of the process by blocking exogenous stimuli that are necessary to launch the chain.

In this review we elaborated on the accumulating and converging evidence from epidemiological studies that strongly suggests that cannabis use during adolescence plays a causal role in the development of persistent psychotic disorders later in life. Although an alternative explanation would be that schizophrenia-prone subjects may consume more cannabis during adolescent development because of the presence of muted forms of psychosis-related behavior, this discussion is beyond the scope of our review. The issue of causality has been extensively discussed in numerous epidemiological studies and reviews (e.g. [Arseneault et al., 2004](#); [Moore et al., 2007](#)) and all suggest a causal link between cannabis use and the risk of developing schizophrenia. Elucidating the underlying neurobiological processes will enhance understanding of this causal relationship and will provide testable hypotheses for future experimental research.

7.1. Future research

Based on the present model, suggestions can be made for future research on neurobiological mechanisms underlying cannabis-induced schizophrenia. First, studies are needed to investigate the respective contributions of excitatory and inhibitory synapses and the involvement of the endogenous cannabinoid system to the experience-dependent refinement of neural circuitries in the prefrontal cortex during adolescence. Although it is most obvious that final refinement during adolescence in the PFC happens at synapses where subcortico-cortical and cortico-cortical neurons merge with pyramidal NMDA-receptors, this still has to be proven. Future studies should especially be aimed at dose and specific time-window of cannabis exposure and the structural changes that it causes in specific areas within the PFC.

Notably, much research has focused on studying the heredity of schizophrenia in family and twin studies, but there are no studies

in which the results of family and twin studies have been combined with those of early cannabis use. In particular, results of such studies can elucidate the contribution of cannabis-induced schizophrenia at population level. More and more epidemiological data become available, but important information about the exact period and amount of exposure is still missing. New prospective studies might shed more light on this matter, when these factors will be taken into account in the design of the studies.

Since the described model stresses that cannabis use during adolescence is critical in the development of schizophrenia later in life, epidemiological studies distinguishing use of cannabis during and after adolescence could confirm the assumptions made in the present model. Most of the research on the neurobiological basis of schizophrenia is monodisciplinary and the same applies to the study of the action and function of endogenous cannabinoids, although both require a multidisciplinary approach. The current model represents an attempt to construct a coherent multidisciplinary framework based on the results from various monodisciplines.

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