Well-being and co-morbidity in recent onset schizophrenia
van Nimwegen, L.J.M.

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Adolescence, schizophrenia and drug abuse: a window of vulnerability


Lonneke van Nimwegen, Lieuwe de Haan, Nico van Beveren, Wim van den Brink, Don Linszen.
Abstract

Objective To discuss the neurobiological and psychosocial developmental factors in adolescence contributing to simultaneous onset and co-occurrence of psychosis and substance use disorders.

Method A review of the literature.

Results Adolescence is a period with specific psychosocial challenges and specific changes in the brain that increase the probability of the onset of both psychosis and substance abuse, in predisposed people. In vulnerable adolescents it is proposed that an excessive pruning of dopaminergic neurones leads to mesocortical hypofrontality causing anhedonia and dysphoria. At the same time, anhedonia and dysphoria are important risk factors for the development of substance abuse. In turn, hypofrontality leads to a reduction in mesocortical feedback inhibition of the mesolimbic system resulting in aberrant salience and positive symptoms. Finally, the development of aberrant salience plays a role in both psychoses and craving.

Conclusion Attention should be paid to the interaction of drug abuse and schizophrenia and an integrated treatment is needed. Dysphoria and anhedonia in schizophrenic adolescents are important factors in treatment with antipsychotic medication, both in terms of patient satisfaction and in the prevention of substance abuse.
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Introduction

Adolescence is the period in human life characterized by a transition to both final brain maturation and independent adult social functioning. Environmental stressors interacting with brain changes and functioning are thought to be risk factors (“hits”) for the onset of psychiatric disorders, e.g. psychoses and substance use disorders. Chambers et al (2003) described adolescence as a critical period for the neurodevelopment of brain regions associated with impulsivity, motivation and addiction. They also hold neuropathology in these circuits responsible for substance abuse comorbidity in schizophrenia (Chambers et al 2001). Recent studies have shown a high prevalence of substance abuse in schizophrenia (Cuffel 1992, Fowler et al 1998, Weiser et al 2003). By stimulating dopaminergic circuits directly (cocaine) or indirectly (cannabis) illicit drugs interact with psychosis. In this review we will focus on neurobiological explanations. Various neurotransmitters (Takeuchi et al 2000) are involved in the onset and course of psychosis and addiction. The glutamatergic system and the N-methyl-d-aspartate (NMDA) receptor have recently gained more emphasis in the onset and course of schizophrenia (Goff and Coyle 2001) and addiction (Kenny and Markou 2004). It is hypothesized that cortical glutamate/NMDA deficiency might cause the cognitive and negative symptoms in schizophrenia and an increased dopamine release in the mesolimbic system might cause the positive symptoms. Clinically however, the co-occurrence of drug abuse and schizophrenia is manifested in an increased probability of psychotic episodes with mainly positive symptoms. In this chapter, we will focus on the dopaminergic system as it is well studied and known to play a role in development of both psychosis and addiction, and because all currently available antipsychotics are dopamine antagonists. We attribute cognitive and negative symptoms to hypodopaminergia in the mesocortical circuits, although these symptoms may also be attributed to hypoglutamatergic states (Heresco-Levy et al 1999, Javitt and Zukin 1991, Krystal et al 1994, Olney and Farber 1995).

Aims of the study

In this review of the literature we discuss what makes adolescents more vulnerable to psychosis and drug abuse. We also will examine the interaction of both vulnerabilities. Finally, we will summarise our findings and consider the consequences of this interaction for research and treatment.
Material and methods

Literature search on Pubmed, using the following keywords: adolescence, neurodevelopment, psychosis, schizophrenia, dopamine, drug use (cannabis, amphetamine, cocaine).

Results

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Epidemiology. Whereas the beginning of the developmental processes that ultimately lead to schizophrenia lies in utero or at birth (Maynard et al 2001, Weinberger 1995), the first psychotic episode generally occurs in late adolescence or early adulthood (Häfner 2003). Males have their first onset at age 15–25 years, females at age 15–29 years (Hambrecht and Häfner 1997).

Psychosocial aspects. Adolescents appear to show an increase of anhedonia (Larson and Richards 1994, Larson et al 2002). They seem to attain less positive impact from stimuli with moderate to low incentive value. Anhedonia can be defined as a psychological condition characterized by inability to experience pleasure in normally pleasurable acts, and is related to the concept of dysphoria, which can be defined as a state of feeling unwell or unhappy. Anhedonia is associated with predisposition to psychosis (Gelber et al 2004, Katsanis et al 1990) and lower functioning in adolescent-onset schizophrenia (Paillere-Martinot 2000).

Neurobiological aspects. The aetiology of schizophrenia has been linked to dysfunctional connectivity (Burns 2003). Functional networks may become incompletely, falsely or overly connected during ontogeny (Brüne 2004). Genetic factors causing adverse effects occurring early during foetal cell migration may become clinically manifest in adolescence or early adulthood when myelinization is completed (Randal 1998). It has been suggested that schizophrenia might arise from abnormal synaptic "pruning" during adolescence (Feinberg 1983, Keshavan et al 1994). During normal development of the brain in early age, the synapses and dendrites that are used most often and are beneficial for it’s functioning are maintained for the adult brain. Connections that are not used enough or that are not beneficial disappear (Jeffery and Reid 1997, Weickert and Weinberger 1998). Especially during adolescence a reorganization of connections takes place through pruning (Keshavan et al 1994). Up to 35% of the maximum level of synaptic density is eliminated during normal development. Psychotic disorders are thought to be elicited by exaggerated pruning during adolescence. McGlashan and Hoffman
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(2000) described a neural network computer simulation of auditory hallucinations. It is a simulation featuring a verbal working memory component with linguistic expectations built up from prior exposure, programmed to process degraded input signals into identifiable words. “Hallucinations” are defined as generated words during periods of input silence. Correct input identification increased when up to 30% of “synapses” were eliminated. Pruning above 35% produced progressive impairment and at higher levels (more than 40%) of pruning hallucinations were simulated. At levels of 65% of synapses eliminated hallucinations decreased. Thus, if a brain is equipped with limited synaptic density to start with in early childhood due to genetic/perinatal factors, and/or if it suffers from an excessive pruning in adolescence (McGlashan and Hoffman, 2000), it would be prone to the development of psychosis after more than 35% of the synapses are lost (Hoffman and McGlashan 1997). The first process in this model consists of structural reductions of connectivity leading to anhedonia/dysphoria. The second neurobiological process in this model is neuromodulatory (dopaminergic) in nature and involves the alteration of the excitability of neuronal elements. These processes are assumed to be relatively independent, i.e. by altering the “bias” or “excitability” of the memory neuronal elements; hallucinations could be eliminated, while cognitive impairments remain unchanged. These alterations are suggestive of receptor-mediated neuromodulatory drug treatment, reversing the positive symptoms, but hardly affecting the cognitive deficits. McGlashan and Hoffmann (2000) predict from this altered neuromodulatory process that the focus of psychotogenic synaptic reductions lies in the working memory systems (e.g. prefrontal cortex). A lack of internal representation of contextual information, resulting from a disruption in the dopamine supply of the prefrontal cortex, brings about deficits in several attention and language-related tasks (Cohen and Servan-Schreiber 1992). The exaggerated pruning hypothesis is interesting because it provides a simple explanation why the illness first manifests itself mostly during adolescence and a neuromodulatory defect in dopamine as a consequence, might explain the various symptoms in schizophrenia. Weinberger (1987, 1995) argues that the interaction of early maldevelopment in utero (“first hit”) with late-maturing adolescent systems (“second hit”), in the prefrontal cortex, limbic system and their connectivity might be an explanation for the delay between early developmental abnormalities and the onset of the disease. An excessive elimination of synapses in the prefrontal cortex, and the parahippocampal region/cortex (Pantelis et al 2003) could underlie this process (Feinberg 1983), causing a decreased dopamine (DA) function in the prefrontal cortex. This leads to mesolimbic DA overactivity, as a result of reduced inhibitory feedback, ultimately leading to positive symptoms of schizophrenia. Kapur (2003) proposed that the central role of dopamine is to mediate the “salience” of environmental events and
internal representations and that a hyperdopaminergic mesolimbic state leads to an aberrant assignment of salience. Kapur suggested that delusions are an effort of a dysfunctional system to make sense of aberrant experiences whereas hallucinations reflect a direct experience of the aberrant salience of internal representations (Kapur 2003). The orbitofrontal cortex (OFC) is involved in perseveration of thought and obsessive–compulsive disorders (Aouizerate et al 2004). It may also explain some of the symptoms in schizophrenia according to the model proposed by Kapur (2003). The same system of salience attribution seems to be involved in the craving for drugs, as we will discuss later.

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**Psychosocial aspects.** Human adolescents exhibit increases in social behaviour, as well as disproportionate amounts of reckless behaviour, sensation seeking and risk-taking relative to individuals at other ages (Arnett 1992). Evolutionarily, this can be viewed as the best behaviour to avoid inbreeding. It makes the adolescent ready to leave the nest and look for a sexual partner far from the genetic-like offspring. Laviola et al (2003) found that adolescent rodents exhibit an unbalanced and extreme-oriented behaviour, consisting of increased novelty seeking, together with decreased novelty-induced stress and anxiety, an increased risk-taking behaviour, as well as elevated levels of impulsivity and restlessness. The characteristics of the adolescents that stimulate explorative behaviour are the same characteristics that might be leading them to experimenting with drugs. The explorative behaviour of adolescents brings them closer to places where drugs are available, and curiosity and impulsivity makes them experimenting with drugs without foreseeing possible consequences. Pleasure seeking and drug use among the adolescent peer group, together with risk-taking behaviour and early initiation in sexual relationships are found to be correlated in several studies (Li et al 2001, Saiz et al 2003, Stanton et al 2001). Sensation seeking might be a reaction to anhedonia, i.e. anhedonic people are unable to enjoy common positive reinforcers and start searching for
Neurobiological aspects. Electrical stimulation of the pleasure reward system leads to intense self-stimulation in animals and, in humans, produces intense pleasure or euphoria (Gardner and Vorel 1998). This circuit is implicated in the pleasures produced by natural rewards (e.g., food, sex) or by psychoactive drugs. The anticipation of the euphoric effect of the drug, the craving, is one of the characteristics of drug abuse and addiction. Childress et al (1999) used positive emission tomography in detoxified cocaine users and found that limbic activation is one component of cue-induced cocaine craving. They suggested that limbic activation may similarly be involved in appetitive craving for other drugs and for natural rewards. The anatomical core of the reward system consists of dopaminergic neurones of the ventral tegmentum that project to the nucleus accumbens, which is described as site for motivation to action. It is the phasic dopamine release in unexpected situations that lead to the rewarding effects with highest impact (Schultz 2001). The projections to the OFC, the prefrontal cortex and the anterior cingulate gyrus are activated in addicted subjects during intoxication and craving, and they are deactivated during withdrawal. The cognitive and emotional processes involved in these structures result in the overvaluing (salience attribution) to drug reinforcers (OFC), craving and compulsive drug administration. It also results in deficits in inhibitory control over drug taking (prefrontal cortex) (Goldstein and Volkow 2002). Why would young people be more vulnerable to drugs than adults? The adolescent brain is a brain in transition. Prominent among the brain regions undergoing developmental change during adolescence are the prefrontal cortex and other forebrain dopamine projection fields. These stressor-sensitive areas form part of the neuronal circuitry modulating the motivational value of drugs of abuse and other reinforcing stimuli (salience). Another component of the liability for early age onset of substance use disorder is neurobehavioural disinhibition (Goldstein and Volkow 2002, Tarter et al 2003). This disinhibition can be defined as a deficient capacity to control behaviour and regulate emotion, and is specific for the brain that is in transition to adulthood. Chambers et al (2003) described preclinical and clinical data supporting that the adolescent neurodevelopmental phase is a biologically critical period of greater vulnerability for experimentation with substances and acquisition of substance use disorders. The idea of Laviola et al (2003) is that a low basal dopamine level in the mesolimbic system of adolescent rodents is similar to that in human adolescents,
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and this too leads to an explanation of the vulnerability to drug abuse in this group and explains the emergence of dysphoria. This low dopamine level possibly causes boredom and dissatisfaction, typical features of human adolescence. But, in reaction to environmental and/or pharmacological challenges, these neurones with low basal dopamine release larger amounts of dopamine compared with adulthood. This would make the positive reinforcing properties of psychoactive drugs even larger in adolescents, than they already are in adults. This hypodopaminergic state was also found during withdrawal in drug abusers, and it is assumed to result in a decreased sensitivity to natural reinforcers, perpetuating the use of drugs as a means to compensate for this deficit and contributing to the anhedonia and dysphoria seen during withdrawal (Volkow et al 2003). Chefer et al (2003) showed that basal DA uptake and release are reduced in individuals who exhibit greater activity in an open field and an enhanced behavioural response to cocaine. Their findings indicated an inverse relationship between basal DA dynamics and responsiveness to novelty and cocaine. This could mean that the (more exploring) adolescent with low basal dopamine levels show more responsiveness to cocaine. Adriani et al (2003) found in rodents that adolescence seems to be characterized by enhanced neurobehavioral vulnerability to nicotine, by way of the same pathways as others drugs. Ameri (1999) showed that psychoactive cannabinoids increase the activity of dopaminergic neurones in the ventral tegmental area – mesolimbic pathway (the reward pathway). The enhanced dopaminergic drive elicited by the cannabinoids is thought to underlie the reinforcing and abuse properties of marijuana.

The interplay between (cannabis) addiction and psychosis

Epidemiology. Examining the interplay of psychosis with drug abuse, and particularly cannabis abuse, most studies report a positive association between prior cannabis consumption and the onset of psychosis (Andreason et al 1987, Arsenault et al 2004, Dixon et al 1991, Goff and Doyle 2001, Longhurst et al 1997, Mathers et al 1991, Rolfe et al 1993, Schneier and Siris 1987, Weiser et al 2003). In addition, Linszen et al (1994) found that cannabis abuse and particularly heavy abuse can be a stressor-eliciting relapse in patients with schizophrenia and related disorders. Based on a review of several studies, Murray et al (2003) concluded that persons vulnerable to psychiatric disorder are more likely to abuse cannabis than the rest of the population, but that heavy abuse of cannabis also acts as an independent risk factor for psychosis. Heavy abuse of cannabis cannot only cause a brief psychotic reaction but probably also acts as a further risk factor in those with a biological predisposition for psychosis. In both adolescents and adults, psychoactive substance use is strongly associated with psychiatric morbidity. A number of studies
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Psychosocial aspects. The self-medication hypothesis postulates that patients with schizophrenia select specific substances to alleviate anhedonia or dysphoria (Mueser et al 1998), or to counteract the side-effects related to the dopamine D_{2} blockade of antipsychotic drugs. The fact that some schizophrenic patients live in low social conditions may also play a role. Lack of activity or unemployment aggravates boredom and increases the need for drug use. Personality traits (Arndt et al 1992, Devaux et al 2001) such as high impulsivity and sensation seeking are also associated with substance abuse in patients with schizophrenia. A high level of sensation seeking can either be an inborn temperamental trait or a later adaptation or reaction to high levels of pre-existing anhedonia. Finally, the label “addict” is by some persons preferred over the label “crazy”.

Neurobiological aspects. Delta-9-tetrahydrocannabinol (Δ^{9}-THC), the principal active metabolite of cannabis, increases the release of dopamine from the nucleus accumbens and prefrontal cortex and raises the level of cerebral dopamine, via the stimulation of the ventral tegmental area. Therefore, low basal dopamine in adolescents and especially low levels of dopamine in the prefrontal cortex in schizophrenic patients is counteracted by the use of Δ^{9}-THC. Drug abuse in the adolescence might be associated with schizophrenia in several ways. Chambers et al (2001) hypothesized that abnormalities in the hippocampal formation and frontal cortex (as seen in schizophrenia) facilitate the positive reinforcing effects of drug reward and reduce inhibitory control over drug-seeking behaviour. Altered integration of dopamine and glutamate signalling in the nucleus accumbens resulting from frontal cortical and hippocampal dysfunction would produce neural and motivational changes similar to long-term substance abuse but without the necessity of prior drug exposure. This means that the brain of a schizophrenic patient resembles that of the (anhedonic) addicted brain, without drug exposure. Drugs like cannabis (Voruganti et al 2001) and amphetamine (Lillrank et al 1991) profoundly affect the brain dopaminergic systems. Continuous amphetamine administration may reproduce some aspects of
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the prolonged excitation, which accompanies an acute psychotic episode (Ellison and Eison 1983), and the use of methamphetamine induces a lasting change in the brain that produces and maintains a schizophrenia-like paranoid psychotic state (Sato et al 1992).

Discussion

Patients with schizophrenia are more likely to use substances than the general population. Schizophrenia and substance use disorders do not only frequently co-exist but also seem to manifest their first symptoms in adolescence. In this review, we argue that it is likely that adolescence is a period in which the psychosocial development (anhedonia and sensation seeking) as well as the specific processes of the developing brain increases the risk of both a psychotic episode and substance abuse disorders in predisposed people. In vulnerable adolescents an excessive pruning of dopaminergic neurones takes place in the frontal brain areas, leading to hypofrontality with increased risk on cognitive disorders, negative symptoms and anhedonia/dysphoria. Following this dopaminergic hypofrontality a reactive neuromodulatory process leads to a dysregulated hyperdopaminergic mesolimbic state, which in turn leads to aberrantly salient experiences such as preoccupations with hallucinations and delusions. The salience of these sensations and thoughts and the inability to switch to other stimuli (as a dysfunction in the OFC) seems to be responsible for the chronic nature of many of these symptoms. A similar problem of salience and inflexibility is present in patients with a substance use disorder. However, here the problem is often identified as craving leading to relapse after period of abstinence and probably responsible for the chronic relapsing course of the disorders; a course very similar to the one observed in many patients with schizophrenia. Resuming, the schizophrenic brain resembles that of the (anhedonic) addicted brain, without drug exposure, i.e. a brain characterized by dopaminergic cortical hypofrontality. Based on the above analysis, an integrated dual diagnosis treatment of schizophrenia and drug abuse is needed. Psychosocial interventions and psycho-education about drug abuse and the interaction with schizophrenia have shown to be fruitful (Shaner et al 2003). Special attention should be paid to dysphoria/anhedonia in schizophrenia.

Antipsychotic medication may contribute to dysphoria and anhedonia. Therefore it is of outmost importance to optimize antipsychotic medication taking in account the subjective experience of the patient. Antagonism of dopaminergic transmission is relevant for this subjective experience, and neuroleptic dysphoria might be a consequence of impaired dopamine function in the nucleus accumbens and plays
Preliminary evidence exists that a window of D₂ receptor occupancy between 60 and 70% is optimal for the subjective experience of patients (de Haan et al. 2004). Levels above 70% D₂ receptor occupancy are associated with negative subjective experience, and D₂ receptor occupancy levels below 60% leaves the patient in a psychotic state, that is also accompanied with negative subjective well-being. High occupancy levels are already reached by using low dosages of antipsychotic drugs (de Haan et al. 2003). Reaching optimum dopamine D₂ receptor occupancy is clinically relevant as subjective experience during treatment with antipsychotic medication is associated with medication compliance and quality of life. Research is needed on the effects of antipsychotics on subjective well-being (Naber 1998, Naber et al. 2001, Voruganti et al. 2004) and on craving for drugs (Hutchison et al. 2003, Smelson et al. 2002). If subjective well-being during treatment with certain neuroleptics is high, it is to be expected that craving for drugs is reduced. Well-designed and controlled studies in antipsychotics to improve subjective experience and quality of life are urgently needed (Awad and Voruganti 2004).
References


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