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Neurocognition and Social Cognition in Middle-Aged and Older Adult Drug Users: Vulnerability and Consequences

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Summary

Although drug misuse in people above middle age is not unusual, relatively little is known about the effects of this on their brain and the consequences as they age. Cognitive function may be a useful indicator for wellbeing in clinical populations and ageing and chronic drug misuse produce similar deficits in cognitive abilities such as problems with maintaining and manipulating information in working memory or attentional difficulties. However, whether there is a combined effect of ageing and drug abuse on brain function, or if these act as separate mechanisms, is not known. This review addresses these issues by contrasting existing knowledge of the effects of drug misuse with those of ageing.

1. Substance abuse in middle and older aged individuals

Although initiation of drug use generally occurs during adolescence, and in many cases 'matures out' during adulthood (Labouvie, 1996), in some heavy drug users, drug consumption continues into late adulthood. Drug use in adolescence increases the risk of problem drug use later in life (Kirisci et al., 2005), because once addiction has been established, it may endure across a lifetime (Culverhouse et al., 2005). Neuroscientific research has been elucidating the neurobiological underpinnings of drug addiction, highlighted in the recent Foresight report *Drugs and the Future* (Nutt et al., 2006). The numerous drug-induced adaptations at the molecular and cellular levels are thought to account for both the stability and persistence of drug using habits over time and the long-lasting vulnerability to relapse, even after many years of abstinence (Nutt et al., 2006).

In addition to the evidence from early adolescence drug use, cross-sectional studies also indicate that many individuals become alcohol dependent after middle age following stressful life events (Atkinson, 1994). Health survey data has shown that the heaviest alcohol drinkers and tobacco smokers in England are aged 55-64 (Blake et al., 2004), but the prevalence of substance abuse in the older population is largely underestimated and under-reported (Rosenberg, 1995). The reasons for this underestimation of drug use in older people are diverse. For example, the signs and symptoms of abuse in the elderly may differ from those seen in younger people (Patterson and Jeste, 1999a). Moreover, the instruments for diagnosing and screening substance misuse may not be sensitive in older individuals (Benshoff et al., 2003), and older individuals may also be less inclined to report drug-related problems due to fear of stigma (Gossop, 2008).

On the other hand, the types of substances abused are likely to differ between generations. For example, illicit drug taking and polydrug use appear to be more prevalent in young people, whereas in the older population, the abuse of alcohol and prescription drugs seems to be more common (Patterson and Jeste, 1999b). In particular, the abuse of prescription and over-the-counter drugs in the older generation (who actually consume one third of prescribed drugs) occurs almost unrecognised and is largely left untreated (Gossop, 2008). Moreover, data from admissions to emergency services suggest that the number of older people consuming illicit drugs is on the rise (Rockett et al., 2006). Correspondingly, the increase of maintenance treatment with methadone and other substitutes over the past decade has been successfully reducing drug-related fatalities, enabling drug users to grow old on prescribed substitute drugs (Gossop, 2008).

Given the increased use of drugs in the older generation and our growing knowledge of the neurobiological changes leading to drug addiction and its long-lasting impact on brain function, it may seem surprising that relatively little is known about how drug use affects ageing. This is an increasing concern since the number of older drug users is expected to rise significantly when the 'baby boomer' generation reaches retirement age (Gfroerer et al., 2003b; Patterson and Jeste, 1999c; Reinhardt, 2000), as this cohort has more drug misuse than any generation before (Boeri et al., 2006). In other words, these individuals are likely to show a wider spectrum of drug problems than currently seen in older adults, which will have a substantial

impact on health care demands of older people in the future (Blow et al., 2002). Whilst psychiatric disorders such as anxiety and depression often co-occur with substance abuse irrespective of drug users' age, medical conditions are known to increase with both age and drug abuse. Consequently, older drug users may require similar psychiatric support to younger drug users, but closer and more thorough medical monitoring. However, the accommodation of older drug users' needs is likely to prove difficult for drug treatment services, as many of them have primarily or exclusively dealt with younger people's drug problems (Gfroerer et al., 2003a). The setting up of specialised drug treatment services for people aged 65+ may therefore be an alternative worth considering.

Drug users' cognitive function plays an important role in the effectiveness of substance abuse treatment: those with cognitive impairments are more likely to show less engagement in the treatment process (Aharonovich et al., 2003b; Teichner et al., 2001). Special treatment strategies may therefore be required for older drug users who are likely to show severe cognitive impairment as a result of both long-term drug abuse and age-related cognitive decline (Adams, 1999). Adjustment of treatment approaches to the cognitive decline in older drug users may actually be key to therapeutic success. In clinical populations, cognitive impairment has been shown to have a significant impact on the quality of life of patients, as reflected in a reduction in daily activities, loss of interest in social and vocational involvement, and difficulties in maintaining personal hygiene or in holding gainful employment (Rao et al., 1991). In the elderly, cognitive status has shown strong associations with psychosocial function, general health and wellbeing in old age (McGuire et al., 2006; St John et al., 2002). Therefore, cognitive remediation training for cognitively impaired drug users could produce benefits outside the clinical setting. Assessment of cognitive function at treatment entry has also proved to be a valuable resource for predicting the functional outcome of psychiatric patients (e.g. St John et al., 2002). For all these reasons, better knowledge about the long-term effects of drug abuse on cognitive abilities and on the process of ageing would provide valuable information for developing treatment programmes for this particular cohort. This review aims to shed light on cognitive function in older drug users by contrasting existing knowledge of cognitive impairment associated with drug abuse and ageing, and to highlight areas on which research and treatment interventions should be focused.

2. Cognitive impairment in ageing and chronic drug use

Cognitive abilities can be divided into two broad categories, namely 'crystallised' and 'fluid' intelligence (see Gustafsson, 1984). While the former category involves accumulated semantic knowledge and expertise that relies on long-term memory, 'fluid' abilities refer to functions necessary for the execution and performance of behaviour, such as psychomotor speed, attention, episodic and prospective memory.

Ageing and chronic drug abuse produce similar deficits in 'fluid' cognitive abilities as reflected in problems with maintaining and manipulating information in working memory or in attentional difficulties (Bugg et al., 2006; Rogers and Robbins, 2001b). A substantial body of evidence indicates that young drug users already have moderate to severe impairment in executive function – the higher-level cognitive abilities necessary for goal-directed behaviour (Burgess, 1997) – such as planning, decision-making, cognitive flexibility, problem-solving and inhibitory control (e.g. Rogers and Robbins, 2001a). The extent of impairment in drug users may be partly due to harmful consequences of chronic drug consumption (Brown et al., 2000; Tapert et al., 2002), although premorbid features may also exist (Nigg et al., 2004). Poor cognitive function in drug users appears to be long-lasting and is even detectable in recovering drug users following prolonged abstinence (Ersche et al., 2006; Medina et al., 2004).

Although a wide a range of cognitive impairment is known to be associated with chronic drug exposure, substance-specific deficits have also been identified (Ersche and Sahakian, 2007; Verdejo-Garcia et al., 2005). For example, abuse of amphetamines has been associated with impairment in processing feedback, which may cause difficulties in predicting outcome probabilities and decision-making (Paulus et al., 2003).

In opiate users, by contrast, the impairment seems to be specific to processing feedback of negative valence, such as errors and punishment (Ersche et al., 2005; Yucel et al., 2007). Chronic alcohol consumption has been shown to exert particularly deleterious effects on the functioning of episodic and working memory (Ambrose et al., 2001; Nixon et al., 1998), which in turn impacts negatively on the learning of associations and on the acquisition of semantic knowledge (Fama et al., 2004; Pitel et al., 2007).

3. Impact of cognitive impairment on functional outcome

Decline of cognitive abilities is a normal consequence of human ageing (Baltes et al., 1999). Converging evidence suggests that 'fluid' abilities, which are largely genetically and biologically determined, are likely to decline with age, while 'crystallised', culture-based abilities seem to remain relatively stable until late in life (see Toga and Thompson, 2005). Models of successful ageing aim to achieve a positive balance between biological decline and cultural growth (Baltes et al., 1999). Regular exercise, social engagement, and a positive mental attitude have been found to be key ingredients for general health and wellbeing in old age (Rowe and Kahn, 1998). Consequently, cognitive impairment is likely to add an additional burden to the already difficult social situations of older people with drug abuse problems (Gurnack and Thomas, 1989).

Poor cognitive function in drug users is likely to have far-reaching consequences. It may limit their ability to benefit from treatment (Aharonovich et al., 2003a; Teichner et al., 2002), may involve difficulties with engaging in vocational activities (Mackin et al., 2005), and may negatively impact on social functioning. For example, the ability to recognise mistakes and to anticipate the magnitude and timing of delivery of rewards plays an important role in learning and in behavioural adjustment to situational demands (Schultz, 2006). Impairment in feedback processing, as observed in chronic users of amphetamines and opiates, may result in maladaptive behaviour which may place a burden on social relationships. Successful social functioning also relies on the ability to interpret non-verbal emotional cues (Carton et al., 1999). Chronic drug users have considerable difficulty in perceiving and understanding affective stimuli such as faces and prosody (Kornreich et al., 2003; Uekermann et al., 2005). In particular, difficulties in decoding facial expressions may result in inappropriate behavioural responses, thereby limiting drug users' abilities in establishing stable social relationships (Kornreich et al., 2001). Impairment in executive function in alcohol-dependent individuals is thought to be directly related to observed deficits in the comprehension of humorous stories (Uekermann et al., 2007). Given the important role of humour in general health, coping and wellbeing (e.g. Kuiper et al., 1992), deficits in this domain are likely to have a negative influence on the quality of life of heavy drinkers. It is conceivable that the negative impact of cognitive impairment on social functioning is particularly hard for older drug users, as their social situation may have become less stable as a result of long-term unemployment, depleted financial resources, lack of family support and social stigma (Center for Substance Abuse Treatment, 2000).

4. Effects of drug and alcohol on ageing brain function

Whether elderly people are more likely to develop cognitive impairment as a result of chronic drug abuse is as yet unknown. Ageing is associated with a variety of biological changes which affect drug disposition and metabolism, and may alter physiological reactions to psychoactive substances (e.g. Mangoni and Jackson, 2004). For example, with ageing there is increased sensitivity and decreased tolerance to alcohol (e.g. Lamy, 1987). Older people also experience greater impairments in psychomotor function with benzodiazepines, mostly due to reduced clearance (e.g. Greenblatt et al., 1991).

However, age-related differences in reactions to psychoactive drugs vary greatly between substances (Dowling et al., 2008). For example, preliminary research finds no evidence for the widely held belief that elderly people are also more sensitive to the effects of opiates (Edwards and Salib, 2002). Rather, it

seems that the duration of action of opiates is prolonged in the elderly, due to age-related differences in pharmacokinetics (e.g. Kornetsky, 2004). Psychostimulants such as amphetamine or cocaine seem to produce qualitatively different effects in older rats than in their younger counterparts (Grilly and Simon, 1994). Similar observations have been made in humans, namely that the performance-enhancing effects of d-amphetamine, such as elevation of mood and alertness, diminish with increasing age, while side-effects such as stereotypy are likely to increase (Clark and Mankikar, 1979). Clinical trials would be needed to systematically evaluate these observations in healthy elderly people.

At present, it is not known whether age-related biological changes predispose elderly people to develop substance abuse (Ozdemir et al., 1996). By contrast, legal drugs such as nicotine and alcohol have been the focus of considerable research, particularly with regard to general health and wellbeing in later life. For the consumption of alcohol, it has been suggested that light-to-moderate daily use in middle-aged and older people might positively affect cognitive abilities, probably by a favourable effect on cardiovascular function (e.g. Palomaki and Kaste, 1993; Zuccala et al., 2001). A considerable number of cross-sectional studies report positive effects of alcohol on cognitive function in old age, but the validity of these results is still a matter of debate. In other words, not all studies find cognitive improvement in light-moderate drinkers (e.g. Meyerhoff et al., 2005), and interactions between cognitive performance, age, and alcohol consumption have not been identified in experimental studies (Schinka et al., 2002). It is likely that variables such as cognitive abilities at baseline, social class, leisure pursuits and amount of social contact mediate some beneficial effects of light-moderate alcohol consumption on cognition in older people (e.g. Elwood et al., 1999). Remember too that a considerable number of elderly people combine alcohol with prescription and/or over the counter drugs, which may lead to severe cognitive impairment (Jorgensen et al., 2001).

While the beneficial effects of alcohol are still under debate, there is, however, widespread agreement on the adverse effects of heavy alcohol consumption on general health and cognitive function (e.g. Moselhy et al., 2001). Yet, somewhat surprisingly, the mechanism by which the harmful effects of chronic alcohol abuse are mediated is still unknown. A review of the literature tentatively suggested that alcohol and ageing have additive adverse effects on cognitive function, most probably through separate neural mechanisms (Glass et al., 1999). One reason for cognitive dysfunction following chronic alcohol exposure in middle-aged adults could be a genetic vulnerability (Anttila et al., 2004). Smoking also has many severe health effects, including cardiovascular and lung diseases, and cancers (Bartecchi et al., 1994). As well as being one of the many agents in tobacco smoke that could be responsible for the harmful effects on general health (Hoffmann and Hoffmann, 1997), nicotine may also have beneficial effects on cognition by enhancing attention (Baron, 1996; Newhouse et al., 2004b). Consequently, nicotinic agonists have become an area of research in drug discovery and development as cognitive enhancers (Buccafusco et al., 2005; Newhouse et al., 2004c). Nicotine seems to enhance cognitive function on tasks requiring effortful processing in healthy, non-smoking volunteers (Ernst et al., 2001; Warburton et al., 1992) – an effect attributed to the stimulation of cholinergic transmission via activation of neuronal nicotinic acetylcholine receptors.

However, this cognitive enhancing effect varies from person to person, probably depending on the integrity of the individual's cholinergic system (Newhouse et al., 2004a). Since cholinergic function declines during normal ageing and is markedly depleted in all forms of dementia, nicotine receptor stimulation may be beneficial by counterbalancing this deficit during cognitive performance (see for review Picciotto and Zoli, 2002). Although lifetime cigarette exposure does not seem to have predictive value for cognitive status in old age (Chen et al., 2003), research *in vitro* and *in vivo* suggests that nicotine may have neuroprotective effects (see Picciotto and Zoli, 2002). These neuroprotective actions of nicotine or nicotinic receptor stimulation are driving the development of pharmacological treatment for neurodegenerative illnesses such as Parkinson's or Alzheimer's disease (Pauly et al., 2004).

In summary, age-related neurobiological changes seem to have an impact on the effects of psychoactive substances in older people. However, the effects on the ageing brain differ across different classes of

substances and the amount consumed (i.e. light, moderate, heavy). Pattern of use (i.e. irregular social use, binge use or chronic consumption) also seems to play a critical role for the behavioural outcome. It is important to note that this knowledge mainly derives from experimental evidence in animals or from healthy human individuals. Studies in older drug users as well as on the influence of chronic drug use on human ageing are still lacking. Comparative studies are, therefore, badly needed to investigate differences in the impact of long-term abuse of illicit drugs such as stimulants and opiates and prolonged exposure to these substances. Where such data exist, e.g. following the use of stimulants for the treatment of Attention Deficit Hyperactivity Disorder and narcolepsy, or opiates for the treatment of chronic pain, there are opportunities to gather data more systematically. This should be encouraged. Insight gained from comparative studies may not only increase our understanding about neuropathological processes but also help to prevent drug-related problems in older adults in the future.

5. Neuropathology associated with ageing, drug abuse and dopamine

Although this is a little studied area, there are reasons for assuming that cognitive deficits in normal ageing and in chronic drug users share a similar neuropathology. The characteristic profile of cognitive deficits in older adults and in drug users is a lack of cognitive control, which is thought to be modulated by a decline in dopamine neurotransmission (Braver and Barch, 2002; Goldstein and Volkow, 2002; Jentsch and Taylor, 1999).

5.1. *Dopamine transmission in normal ageing*

Both the nigrostratal and in particular the mesolimbic dopamine system are susceptible to age-related changes (Cruz-Muros et al., 2007). Age-related reductions in dopamine D1and D2 receptor densities, however, do not seem to be limited to striatal brain areas (Volkow et al., 1998c; Wang et al., 1998). D2 receptor reductions during ageing have also been identified in extrastriatal areas, including the frontal cortex and cingulate cortex (Kaasinen et al., 2000). In the striatum, the age-related decline in the density of D2 receptors (Volkow et al., 1998b) and dopamine transporters (van Dyck et al., 1995; Volkow et al., 1996b) is associated with reduced psychomotor and cognitive performance in healthy adults (Volkow et al., 1998a; Mozley et al., 2001). In fact, the striatal dopamine D2 receptor density has proved to be a strong predictor for cognitive performance in healthy adults, but interestingly, this effect was independent of age (Backman et al., 2000; Volkow et al., 1998d). This may suggest that the variability in cognitive status observed in elderly people may be explained by differences in dopamine D2 receptor density, rather than by the biological age (Backman et al., 2000).

5.2. *Dopamine transmission in substance abuse*

Reduced densities in dopamine D1 and D2 receptors have frequently been reported in chronic users of various addictive drugs (Dagher et al., 2001; Volkow et al., 1993; Volkow et al., 1996a). This abnormality is believed to reflect either a down-regulation of receptors in response to chronic drug exposure (Ginovart et al., 1999) or a pre-morbid vulnerability towards addictive behaviour in general (Dalley et al., 2007; Volkow et al., 1999), or both of these (Nader et al., 2006). The pronounced reduction in striatal dopamine receptors in chronic drug users may resemble an early onset of the ageing process. Indeed, some researchers have suggested that drug users might undergo an accelerated ageing process, as the brains of young stimulant users show abnormalities typically seen during normal ageing (Makris et al., 2004; Thompson et al., 2004). On the other hand, research has also found a lack of the normal age-related decline in dopamine transporter density in chronic drug users (Tupala et al., 2003; Wang et al., 1997), which might be indicative of a pre-existing dopaminergic deficit. Further research is clearly needed to better understand the neuropathology of drug abuse, and in particular to differentiate possible predisposing factors from the consequential effects of chronic drug exposure.

5.3. *Changes in cognitive function associated with ageing and substance abuse*

Given that structural changes in dopamine receptor and transporter density, occurring in both drug users and older people, are likely to affect dopamine-dependent brain function, one may expect that chronic drug users and older adults exhibit similar functional abnormalities and a similar predisposition for addiction. The neurobiological model of addiction suggested by Volkow and colleagues (2003) explains reduced dopamine neurotransmission in the midbrain as a reflection of a decrease in sensitivity to natural rewards and a greater need for stimulation to activate the brain-reward circuitry (Volkow et al., 2002). According to this model, people with a low dopamine receptor density in the striatum have an increased propensity to develop addictive behaviours for two reasons: a) they require a relatively large amounts of psychoactive substances (e.g. alcohol) until they feel intoxicated (Yoder et al., 2005), and b) they experience the effects of stimulant drugs, which directly increase dopamine levels, as pleasurable (Volkow et al., 1999). As a consequence, natural rewards may progressively lose attractiveness and become less powerful in motivating behaviour (Volkow et al., 2003).

The model finds support from neuroimaging studies in chronic drug users showing reduced responsiveness to non drug-related rewards (Goldstein et al., 2007; Sell et al., 1999) and attentional bias towards drug rewards (Franken et al., 2004; Hester et al., 2006). Behavioural studies indicate an age-related reduction in reward sensitivity, as older adults seem to be less influenced by reward (Bellucci and Hoyer, 1975; Sanford, 1978; Tripp and Alsop, 1999) and require more effort to learn reward-associations than their younger counterparts (Mell et al., 2005). According to the model of Volkow and colleagues (Volkow et al., 2003), reduced sensitivity of reward circuits to natural reinforcers, concomitant with decreased activity of cognitive control circuits, increases the individual's vulnerability to develop addiction. Interestingly, the low density of striatal D2 receptors in stimulant users and older adults has been associated with reduced metabolism in the prefrontal cortex (PFC) (Volkow et al., 1993), which is thought to reflect dysfunction in the inhibitory control system (Goldstein and Volkow, 2002). Poor inhibitory control could have detrimental consequences for drug users, as it may limit their ability to resist the strong drive to consume drugs by compromising control over their behaviour (Goldstein and Volkow, 2002). Since older people do not show this heightened sensitivity towards drug rewards, the consequences of poor inhibitory control in them may be far less dramatic than in drug users. Although it is not known whether age-related biological changes predispose elderly people to develop substance abuse, the Volkow model would not predict older people having a heightened vulnerability to addiction.

Functional neuroimaging research shows that, during cognitive performance, task-related activation in the PFC increases when executive control is required (Lau and Passingham, 2007; Rypma et al., 2001). Older adults and chronic drug users consistently exhibit less task-related activation in the PFC during executive processing, compared with younger adults (Rypma et al., 2001) or non-drug users (Hester and Garavan, 2004a; Pfefferbaum et al., 2001). Concomitant with this under-activation of the PFC, older adults and drug users show non-selective recruitment of brain regions that are not typically activated in young or non-drug using individuals, in order to meet task demands (Desmond et al., 2003; Hester and Garavan, 2004b). Cognitive training can ameliorate age-related under-activation in the PFC in older adults (Logan et al., 2002) and in younger individuals when they are specifically instructed to use cognitive strategies (Savage et al., 2001). Therefore, future research should explore whether cognitive training – as well as cognitive enhancing pharmacological agents – can likewise augment task performance in drug users.

6. Potential lines of investigation for treating older drug users

A potential agent for improving cognitive function in older drug users is methylphenidate, a stimulant that blocks the reuptake of dopamine and noradrenaline by their respective transporters (Kuczenski and Segal, 1997). The observation that cocaine users do not show age-related decline in their dopamine transporter

mechanism, may explain why methylphenidate has the potential to increase metabolism in the PFC in cocaine-dependent individuals, while decreasing metabolism in healthy volunteers (Volkow et al., 2005). It is, therefore, conceivable that methylphenidate could improve cognitive function in older cocaine users while showing few effects in healthy elderly people (Turner et al., 2003). Further lines of investigation may include genotyping of candidate genes such as the catechol-O-methyl-transferase (COMT) polymorphisms, which determine the enzyme regulating dopamine turnover in the PFC (Lachman et al., 1996). The val(108/158)met polymorphism has been implicated in working memory function mediated by the PFC (Meyer-Lindenberg et al., 2005), which predicts the modulation of cognitive effects by dopaminergic drugs (Mattay et al., 2003; Weickert et al., 2004). COMT genotyping in older drug users may provide valuable information in two regards: a) for exploring the predictive value of the cognitive decline in this population and the suitability of pharmacological intervention with methylphenidate, and b) for examining a genetic vulnerability for late-onset substance abuse, which in alcoholism has been linked with a dopaminergic dysfunction (Cloninger, 1995).

7. Conclusions

Converging evidence from epidemiological studies and household surveys indicates that abuse of legal and illegal drugs in older individuals is more common than might be expected. The high rates of problem drug use among the baby-boom cohort suggests that the number of problem drug users in the older population will increase as this generation ages; the consequences of this demographic development have been widely underestimated. A growing number of older drug users will require a change in treatment services which currently mainly deal with problem drug use in younger people, shifting the focus to older adults and their needs.

The fact that cognitive function moderates the effectiveness of substance abuse treatment, and that cognitive abilities not only decline with age but are also impaired in chronic drug users, may prove important in the treatment of older drug users. Despite many years of drug addiction research, relatively little is known about the impact of chronic drug abuse on age-related cognitive decline. The variety of neuroscientific methodology available today, including pharmacological and functional neuroimaging, neurocognitive testing and genotyping, may enable us to elucidate the mechanisms mediating the harmful effects of chronic drug and alcohol abuse in older people.

Insights gained from neuroscientific research into ageing processes in drug users may drive forward the development of suitable instruments for screening and diagnosis, and guide future therapeutic interventions to meet the increasing challenge faced by drug treatment services in the light of the growing number of older drug users.

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