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REVIEW

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Nicotine psychobiology: how chronic-dose prospective studies can illuminate some of the theoretical issues from acute-dose research

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Abstract *Rationale:* To illustrate how prospective cigarette smoking research can illuminate some of the theoretical dilemmas about nicotine psychobiology from acute dose research. *Methods and results:* When briefly deprived smokers are administered nicotine, they display a range of psychobiological 'gains', with improved cognitive performance, feelings of contentment, and reduced feelings of stress or depression. However, abstinence leads to decrements in all these functions. The balance between the deficits of nicotine deprivation and the gains of reinstatement has been debated for decades. Yet, it still remains controversial whether nicotine is psychobiologically beneficial, neutral or detrimental. Some illumination may be provided by prospective research. Taking up smoking during adolescence is often followed by increased feelings of stress and depression, whereas quitting is often associated with subsequent mood gains. Short-term prospective studies reveal that the essence of nicotine dependency is repetitive psychobiological vacillation. The mood gains of smoke inhalation represent the temporary reversal of abstinence effects, and the frequent experience of negative states in between cigarettes explains why smoking can increase psychobiological distress. This may also be linked with Diathesis–Stress models. If withdrawal symptoms reflect the exacerbation of natural predispositions, then 'disadvantaged' smokers will suffer the worst abstinence symptoms and develop the strongest nicotine dependency. This explanation contrasts with the self-medication model, which focuses on the immediate benefits of smoke inhalation, rather than the overall costs of nicotine use. *Conclusions:* The frequent experience of negative psychological states in between cigarettes helps to explain why nicotine dependency is associated with a range of psychobiological problems.

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Introduction

In an editorial entitled *Beneficial effects of nicotine: fact or fiction*, West (1993) noted: 'Many smokers report that they enjoy smoking and also that smoking helps them in various ways—particularly controlling stress and maintaining alertness. There seems to be a tacit acceptance by many researchers that smoking has effects that are psychologically beneficial'. Following a brief review of the empirical literature, West (1993) outlined five possible scenarios, which ranged from nicotine having positive effects on performance and stress in all situations to nicotine having no genuine positive effects at any time. Subsequent commentaries agreed that further research was needed to clarify the relative benefits of smoke inhalation, with the relative deficits of nicotine abstinence (Foulds 1994; Spilich 1994). Henningfield (1994) also noted that 'the purported benefits of nicotine self-administration have been the subject of scientific and medical debate during much of the twentieth century'.

Somewhat surprisingly, none of the scenarios outlined by West (1993) included the possibility that nicotine might be psychobiologically damaging. This was despite the prime focus for the editorial being some recent empirical findings by Spilich et al. (1992), where 'smokers were worse at several cognitive tasks than were non-smokers'. West (1993) also noted other findings where cigarette smokers displayed lower levels of psychological well-being than non-smokers, whereas former smokers were similar to non-smokers. This led to the following suggestion that 'Heightened dysphoria only lasts for as long as one smokes and raises the question of whether smoking might even induce psychological distress'. Henningfield (1994) similarly described this possibility, whilst I also noted recent findings of heightened stress in current smokers (Parrott 1994a). However, the main problem for nicotine researchers at that time was the absence for any explanatory model

of how nicotine dependency might cause psychobiological distress.

Since then, many more studies have documented psychobiological impairments in cigarette smokers. Yet most authors continue to be perplexed by their findings. McGee et al (2000) noted that they did not know why taking up smoking during adolescence led to greater stress and depression. Goodman and Capitman (2000) did not offer an explanation to why taking up smoking should lead to increased depressive symptoms. Breslau et al (2005) found that current smoking, but not past smoking, predicted subsequent suicidal behaviours (independently of depression), but they also noted that an 'explanation of the finding… is unclear'. Similar comments have been made by Glass (1990), Wu and Anthony (1999) and in several other prospective studies where smoking uptake led to an increase in psychobiological problems. Ernst et al (2001) found significant memory performance decrements in a working memory task, but also noted that this impairment in memory performance of cigarette smokers was 'surprising', given previous findings of memory benefits following acute nicotine administration (e.g. by Pineda et al. 1998).

The core aim of the current paper is to explain why these psychobiological deficits should not be seen as 'surprising'. In particular, it explains why the chronic use of nicotine can be psychologically damaging despite acute nicotine administration often leading to immediate gains. The essence of nicotine dependency is the repetitive vacillation in psychobiological status. There is a constantly changing balance between the gradual development of abstinence symptoms and cravings and the transitory feelings of relief and contentment on nicotine reinstatement. Only when this balance is fully considered, can it be estimated whether, in overall terms, nicotine is providing psychobiological benefits or exacerbating problems. The following sections will firstly cover the effects of acute nicotine, before moving on to the longer term prospective studies. It will be argued that these latter findings are crucial for providing answers to some of the theoretical dilemmas from acute dose laboratory research.

The explanatory model was originally devised to explain how regular nicotine use could exacerbate stress (Parrott 1999). Various aspects of the model were criticised (Gilbert and McClernon 2000; Kassel 2000; Piasecki and Baker 2000) and I replied to these commentaries (Parrott 2000a). The scope of the model then was broadened to include findings of heightened depression in smokers (Parrott 2003). In this paper, I will include some more recent findings on these two topics, but I will also include data on related issues, for instance on cigarette smoking and suicidal behaviours (Oquendo et al. 2004). Disadvantaged smokers will then be discussed in the context of the Diathesis–Stress model, which has rather different predictions from the Self-Medication model. Finally, I will also debate cognitive functioning. Here, the empirical data are more variable and often differ in subtle but important ways from the mood findings. In particular, there are several lines of evidence for acute gains in some areas of cognitive functioning under certain situations (Newhouse et al. 2004). Nevertheless, these need to be considered against acute withdrawal phenomena, so that again, the overall utility of nicotine can only be revealed in long-term prospective studies.

Acute nicotine effects in smokers

Nicotine reinstatement in briefly deprived smokers often leads to feelings of alertness, satisfaction, relaxation and improved cognitive task performance (Gilbert 1995; Newhouse et al. 2004; Parrott and Craig 1992; Parrott and Garnham 1998; Snyder and Henningfield 1989; Warburton 1992; Wesnes and Parrott 1992; West 1993). This has led to one of the predominant models for nicotine, namely, that it provides acute neurobiological advantages for regular tobacco users. This positive resource model is encapsulated in the following quotation by Hughes (2000, p.xvi) stating that 'Nicotine is a renaissance drug—it can do many things, improve mood, increase concentration, suppress weight and decrease anger'. Dudas and George (2005) similarly noted 'Nicotine provides a number of benefits, including anxiety relief, increased alertness, and improved cognitive functioning'. Positive resource models differ in their complexity, with Warburton (1992) outlining a basic resource model, whereas Gilbert (1995) outlined a far more complex set of propositions. My own nicotine research was originally based on this tradition (Parrott 1992). It employed the predominant laboratory design, where nicotine is administered to briefly deprived regular smokers via tobacco restoration or nicotine gum, the control condition being continued abstinence or placebo gum (Parrott and Craig 1992, Parrott and Roberts 1991; Parrott and Winder 1989). The emergent findings were similar to those of previous groups (Snyder and Henningfield 1989; Wesnes and Warburton 1987) in showing that nicotine reinstatement led to a variety of psychobiological gains. These and many similar findings have provided empirical support for a wide range of nicotine resource models (Gilbert 1995; Parrott 1992; Hughes 2000; Warburton 1988, 1992; Wesnes and Parrott 1992; Wesnes and Warburton 1987). Indeed under certain circumstances, nicotine can display beneficial cognitive properties (Dudas and George 2005; Sacco et al. 2005). However, these benefits may be limited to certain functions or to (psychiatric) subgroups with low baseline performance levels (Newhouse et al. 2004).

Prospective psychobiological effects of smoking in adolescence

Cross-sectional comparisons of adolescent cigarette smokers and non-smokers, show that smokers often display a higher incidence of stress, depression, suicidal behaviour, poor self-esteem, low self-efficacy and other psychobiological problems (Gilbert 1995; Lloyd and Lucas 1997; Mitic et al. 1985; Malone et al. 2003; Patton et al. 1998). This cross-sectional evidence, however, is inherently limited because the self-selected groups come from different background populations. For instance, smokers and non-

smokers may differ constitutionally in personality dimensions, socioeconomic class, genotypic profile, or their experience of environmental stressors (Surgeon General 1988, 1990). There may also be genetic linkages between aspects of nicotine dependency and these other non-drug factors (Xian et al. 2005).

The clearest evidence on the psychobiological consequences of smoking therefore comes from prospective studies, where large cohorts of adolescents are systematically monitored over time. Using this design, numerous studies have found that the uptake of smoking is psychobiologically damaging. Wu and Anthony (1999) prospectively investigated the relationship between the initiation of tobacco smoking and subsequent depression in 8- to 14-year-old schoolchildren. They found that tobacco use signaled a modest increase in risk for subsequent feelings of depression. Whereas depressed mood at baseline did not increase the risk of taking up smoking in later years. Johnson et al. (2000) investigated the association between cigarette use and anxiety disorders over several years of adolescence and early adulthood. Heavy smoking at 16 years of age, led to an increase in generalised anxiety, agoraphobia, and panic disorders 5 years later. In contrast, high levels of anxiety, whilst aged 16, did not lead to an increased incidence of later smoking. Steuber and Danner (2006) prospectively monitored over 14,000 adolescents to assess the direction of the temporal relationship between smoking and depression. Although cigarette smoking led to more depression in both genders, it was also noted that 'women showed a striking pattern of increases in depression around the onset of smoking and decreases around the time of quitting'. McGee et al (2000) prospectively monitored behavioural problems, mental health ratings and psychoactive drug use in a large cohort of New Zealand young people. Early socioeconomic problems led to an increased probability of initially taking up smoking, furthermore those adolescents who became regular smokers reported increased rates of psychobiological problems at the later time point. Thus, smoking at age 18 'elevated the risk of anxiety/depressive disorder' 3 years later.

Other prospective studies have illuminated further aspects of the relationship between smoking and depression. In a 5-year longitudinal study, Breslau et al (1998) found that daily smoking at baseline led to significantly higher depression in later years, whilst high depression at baseline also led to an increased incidence of later smoking. Escobedo et al. (1998) and Polen et al. (2004) found that depression at baseline predicted the later uptake of smoking. Fergusson et al (2003) found that young people meeting DSM IV criteria for major depression had elevated rates of daily smoking and nicotine dependence. They also noted: 'There is evidence for a possible causal linkage between smoking and depression. The direction of causality between smoking and depression remains unknown'. Oquendo et al (2004) investigated the determinants of suicidal behaviour in a cohort suffering from major depression. Cigarette smoking was found to be one of 'the three most powerful predictors' of suicidal acts, the other factors being previous suicide attempts and the severity of depression; their influence was additive rather than interactive. Anda et al. (1999) found that more adverse childhood events led to greater adult depression, whilst cigarette smoking was an additional determinant; their data also illustrated that these two factors were additive rather than interactive (Parrott 2000b). Goodman and Capitman (2000) confirmed that depressive symptoms and cigarette smoking during adolescence were closely inter-related. Cigarette use at baseline in non-depressed teenagers was found to be a 'powerful determinant' for depressive symptoms 1 year later. This predictive relationship emerged in all their multi-factorial models. Hence, the uptake of smoking led to a significant increase in depressive symptoms 1 year later, and this could not be explained as being due to the influence of other variables (models 1–4 in their Table 3). The effects of depressive symptoms at baseline upon later smoking were more complicated. The initial bi-variate analysis showed that depressive symptoms pre-smoking predicted the later uptake of cigarettes. However, the predictive power of depressive symptoms was steadily reduced in the more complex multi-variate models, as other factors such as 'experimentation with cigarettes' demonstrated greater loadings (see Table 5 in Goodman and Capitman 2000). This should act as a reminder that psychobiological aspects are just one of several determinants for smoking behaviour. Indeed, non-biological factors will often be more important, as was evident with these novice smokers.

Prospective consequences of smoking cessation in adulthood

In a parallel fashion, long-term prospective investigations of adult smokers have typically found that to quit smoking leads to reduced stress. Cohen and Lichtenstein (1990) assessed 211 smokers who stated that they were planning to quit, firstly at baseline, then at 1, 3 and 6 months later. Those who failed to quit (n=57) reported similar high stress at every time point, whereas those who stopped smoking throughout (n=12) reported reducing levels of stress over time. Cohen and Lichtenstein (1990) also analysed the effects of change in smoking status between particular time periods for all the other subgroups (e.g. between 1 and 3 months, also between 3 and 6 months; see their Table 1). Despite often having small sample sizes, they found a very consistent pattern, where for every possible permutation relapse was always associated with increased stress, whereas quitting was always associated with a decrease in stress. In a prospective Australian study, Carey et al. (1993) found that 6 months of complete cessation led to a significant reduction in self-rated feelings of stress. West and Hajek (1997) found significantly reduced levels of anxiety after just a few weeks of biochemically confirmed abstinence. Parrott (1995) found a significant reduction in self-rated stress after 3 and 6 months of confirmed smoking cessation. Self-rated stressful life events remained unchanged in the two groups over the 6 months of cessation; hence, the reduced stress of the successful quitters was not an artefact of change in life events. Hughes (1992) pro-

spectively assessed a broader range of feeling states over a 9-month period. In the immediate post-quitting period, levels of anger, restlessness and anxiety increased noticeably, but over subsequent weeks and months the whole spectrum of mood states improved over those found at baseline. In a longer prospective study, Chassin et al. (2002) found decreased levels of stress 6 years after quitting. When these former smokers were actively smoking, they gave out self-reports of significantly higher levels of stress than the non-smoker control group. Then after successful cessation, their stress levels reverted to the lower levels reported by non-smokers.

Gilbert and McClernon (2000) suggested that this reduction in stress post-quitting might be an artefact of various factors. The first factor is selective relapse, with the more highly stressed smokers having a greater tendency to relapse (Covey et al 1990; Shiffman 1982), leaving the successful quitters with lower stress levels. This is an important potential confounded in both cross-sectional and prospective studies, although the strength of prospective studies is that the baseline data can be scrutinised to see if selective relapse has affected the findings. Cohen and Lichtenstein (1990) examined their data to see if this occurred but found that the initial baseline stress levels were almost identical for successful and unsuccessful quitters. Furthermore, whilst they remained at this same high level in the continuous smokers, they reduced over time in the successful group (see their Fig. 1). It should also be noted that the baseline stress scores for the partially successful group were also similar to the other two groups at baseline (again, see their Fig. 1). The other important factor is stressful life events, as these will often lead to the resumption of smoking. Cohen and Lichtenstein (1990) also examined whether stressful external events led to smoking resumption, or whether smoking relapse led to more perceived stress. They undertook a series of time lag analyses, but 'none provided clarification on the direction of causality'. (Note: this failure to separate out external stressors from internal feeling state changes should not be seen as too surprising because both should be closely linked. Smoking in response to an external stressor may immediately engender a cycle of nicotine-dependent mood vacillation and, hence, greater stress lability; see the explanatory model outlined in the final section). In another prospective cessation study (Parrott 1995), the scores for unsuccessful and successful quitters were almost identical at baseline for perceived stress and neuroticism. So again, it was not the case that those who managed to quit successfully had been less stressed at baseline, nor were they less predisposed to stress. Self-ratings of stressful life events were also assessed, and they remained constant over the 6-month cessation period. So again, the successful quitters had not experienced less stressful circumstances. Selective relapse and stressful life events should however be monitored in all cessation studies because they might act as a source of bias towards finding lower stress levels in the successful quitters.

Gilbert and McClernon (2000) also suggested that self-rated stress levels tend to decrease with repeated measurement, citing several studies where this had been found (e.g. Choquette and Hesselbrock 1987; Gilbert et al. 2002; Hatzenbuehler et al. 1983; Sharpe and Gilbert 1998). Therefore, it is important to examine the generality and robustness of this phenomenon and consider how it might effect prospective nicotine research, not only the adult cessation findings (present section), but also the adolescent initiation literature (previous section). Cohen and Lichtenstein's (1990) data did not show the repeated measurement effect, as their continuing smoker group reported very similar stress levels at 0, 1, 3 and 6 months. Their sub-group, who returned to smoking after a very brief attempt at cessation, also reported similar stress levels over all four time points. In our own studies involving repeated self-ratings, although mood states are certainly very sensitive to circadian effects (Jones and Parrott 1997; Parrott and Kaye 1999), we have not encountered this repeated measurement effect. For instance in Parrott and Garnham (1998), the effect of smoking a cigarette in non-deprived smokers was to leave their self-rated stress levels unchanged (from 3.2 at baseline, to 3.3 post-cigarette). The significant mood relief engendered by smoking a cigarette in the overnight-deprived group (reduced from 5.4 at baseline, to 3.1 post-cigarette) cannot therefore be explained as a repeated measures artefact. Moving to the generality of the phenomenon, it is not described in the instruction manuals for scales such as the Profile of Mood States, Speilberger State/Trait Anxiety Questionnaire, Middlesex Hospital Questionnaire or Short Adjective Checklist. The many studies they cite do not display it, nor have I encountered it during my research into the psychopharmacology of stress and other mood states over 25 years (reviews: Parrott 1985, 2006), nor does it have any theoretical rationale. However, if Gilbert and McClernon (2000) have uncovered a reliable phenomenon, then it should be documented and an explanatory model proposed, as it would have important implications for all areas of mood research. One final question is that if 'repeated measurements' is proposed an explanation for the reduced stress with adult quitters, why do adolescents who take up smoking prospectively report increased stress?

Nicotine dependency: a direct cause of psychobiological distress

One potentially straightforward explanation for how cigarette smoking may cause psychobiological distress is nicotine dependency. This explanatory model has emerged from a series of studies involving the ecologically valid design of smokers self-rating their moods, before and after each cigarette smoked over the day (Parrott 1994b). This design has revealed that smokers experience repetitive mood fluctuations over the day, which correspond directly with their cigarette usage patterns. Smokers who stated that they used cigarettes to control their moods suffered from below-average moods in between cigarettes, and smoke inhalation restored their moods to normal for a brief period.

Comparison with non-smokers showed that smokers did not gain any mood advantages from cigarettes, but instead, suffered repeatedly from abstinence symptoms. Hence, nicotine dependency actually caused increased levels of psychobiological distress (Parrott and Garnham 1998, Parrott and Kaye 1999; Schachter 1978). In a Spanish study, freely-smoking cigarette smokers demonstrated more variable mood states over the day than non-smokers, whilst their mood self-ratings were often worse than non-smoker controls: 'Smokers have suboptimal activation and mood states at certain times even under the influence of multiple doses of nicotine' (Adan and Sanchez-Turet 2000).

The degree of withdrawal distress is related to the heaviness of smoking because these mood fluctuations tend to be strongest in the most dependent smokers (Parrott 1994b). Therefore, heavy smokers report severe abstinence symptoms and corresponding strong feelings of relief upon smoking, which is why they need to smoke so frequently (Parrott 1998, 2000a). Adan et al (2004) confirmed that heavy and light smokers both displayed worse mood profiles than non-smokers, whilst the heavier group reported the worst pre-cigarette moods and the greatest mood normalization post-smoking. Nicotine withdrawal symptoms are also more severe under stressful environmental situations, so that their feelings of relief on nicotine re-instatement are correspondingly stronger when under high levels of external stress (Parrott and Slater 2000). When deprived smokers experience nicotine re-instatement, they can report improved moods and better cognitive performance after just one or two cigarette puffs (Warburton 1992; Revell 1998). With 70,000 reinforcing cigarette puffs each year, this psychobiological relief becomes strongly conditioned and over-learned, which is why nicotine can be such a powerful drug of dependency (Parrott 1999; Parrott et al. 2004). However, it should also be noted that around 15% of smokers only use cigarettes intermittently. These "chippers" generally report neither mood decrements when they abstain, nor mood gains when they smoke (Shiffman 1989). Although some light smokers occasionally report mood changes (Parrott 1994b), their limited occurrence may help to explain how they can remain as occasional smokers (Parrott 1998, 1999). It should be noted that these cross-sectional studies involve many different types of smokers and non-smokers, and that any differences in genetic, constitutional, and personality profiles (see earlier), may contribute to the between-group findings.

Nevertheless, it can be proposed that nicotine dependency is a direct, albeit subtle, cause of psychobiological distress (Parrott 1999, 2003). The repeated experience of adverse psychobiological states many times over the day directly causes the worse daily moods of many tobacco smokers. Once nicotine is conceptualised as a drug of dependency, its behavioural, cognitive and emotional effects become straightforward to understand. The need to forestall abstinence symptoms explains why smokers follow such regular patterns of cigarette consumption over the day (Parrott et al. 1996). Furthermore, cigarette use only generates mood changes in nicotine deprived smokers, so that when non-deprived smokers have a cigarette, their mood self-ratings remain unaltered (Parrott and Garnham 1998). Indeed, nicotine can be aversive when given to non-deprived regular smokers (Perkins et al. 1997). In regular smokers, the subjective feeling state changes can be quite subtle, with only slight feelings of irritation during early abstinence, so that its normative/restorative effects can be difficult to describe. However, feelings of 'relief' or 'contentment' can describe the reversal of mild withdrawal symptoms, whilst 'craving' describes the urgent need to restore normality after longer periods without nicotine.

In a recent review of nicotine withdrawal symptoms and tobacco cravings, Shiftman et al. (2004) noted its heterogeneous nature. Many different symptoms can be experienced (see next paragraph), but it was noted that they also tend to vary between individuals and over time. There was a recommendation to establish a more robust and reliable set of assessment measures, but this may be difficult because of their individual and temporal variation. Mood lability is at the core of nicotine dependency and develops with longer periods of acute withdrawal (Fant et al. 1995; Parrott et al. 2000), but many personality and environmental factors further influence them. Smoking abstinence symptoms also follow general trends but can be subject to many other influences, making them difficult to predict. Marlatt has integrated aspects of Buddhist Philosophy with Californian modes of transport to describe 'urge surfing'. Here, drug cravings can build up to intensive levels, but then they may dissipate with equal rapidity (e.g. Witkiewitz and Marlatt 2004). In the longer term, nicotine cravings tend to peak over the first few days. They often remain strong for several weeks, but gradually diminish over the ensuing months of cessation (Hughes 1992). This pattern can be quite variable, so that some smokers can get over their withdrawal symptoms quite rapidly, whereas heavy smokers in particular can experience them for far longer periods (Gilbert et al. 1999; Shiffman et al. 2004). Indeed, nicotine cravings can still occur many years after quitting, and may emerge particularly under situations of high environmental stress (Surgeon General 1990). Finally, one limitation with the nicotine withdrawal literature is its focus on negative experiences (Shiffman et al. 2004). Perhaps this is another reflection of the prevailing nicotine resource model. Therefore, one improvement to current cessation measures would be to include more positive scales, for instance on the long-term benefits to self-efficacy, contentment, satisfaction, happiness, relaxation and reduced mood lability. These should all gain in prominence over time—as long as cessation is maintained.

This explanatory model, based on the adverse psychobiological effects of nicotine withdrawal in current smokers, can help to explain why smoking has such a variety of seemingly contradictory effects. Nesbitt's (1973) paradox is readily explained. The positive resource model generates the apparent paradox that tobacco smoking can increase arousal and decrease stress at the same time. The negative resource model notes that regular smokers feel tired and stressed without nicotine, and the next cigarette

normalises both cortical arousal and emotional tension in parallel (Parrott 1998). The negative resource model can also explain why the first cigarette of the day is the most 'satisfying' (Parrott 1998, 1999) because the degree of satisfaction is directly related to the duration of prior abstinence (Fant et al. 1995). Nicotine dependency can explain why so many different psychobiological functions are impaired in cigarette smokers. Heffernan et al. (2005) showed that prospective memory ability was significantly impaired in smokers compared to non-smokers, with the greatest decrements amongst the heaviest smokers (see later). Sleep is often impaired in tobacco smokers (Wetter and Young 1994), whilst the sleep of former smokers shows significant improvements 6 months after quitting (Wolter et al. 1997). Central nervous system stimulant drugs can adversely affect sleep and may impinge on the transition between sleep and wakefulness through alterations in various neurochemical/neuromodulator systems, including the cholinergic (Boutrel and Koob 2004). Falling plasma nicotine levels over the night, and hence increasing nicotine withdrawal, may be a primary causative factor for the disturbed sleep. Smokers also tend to suffer from low self-esteem, and guilt about their nicotine dependency. Self-efficacy is also impaired because when faced with problems, smokers often light up a cigarette to feel better instead of directly tackling the problem, an avoidance strategy also evident in child smokers (Lloyd and Lucas 1997). Finally, whilst nicotine dependency causes mood lability, there is evidence for neurocognitive gains under some circumstances. This topic will now be examined in the context of the self-medication model.

Self-medication model

The proportion of tobacco smokers amongst those with psychiatric disorders is often higher than amongst the 'normal' population. Furthermore, cigarette use in schizophrenic, depressed and some other clinical populations is typically heavier, with more cigarettes smoked per day, more intensive patterns of inhalation and greater difficulty in quitting (Beckham et al. 1997; Hughes et al. 1986; Piasecki and Newhouse 2000; Sacco et al. 2005; Lasser et al. 2000; but also see Alves et al. 2005). This has led to the notion of self-medication, where smokers are hypothesised to be using nicotine to relieve some of their neurocognitive problems. Sacco et al. (2005) noted: 'In a number of neuropsychiatric disorders [e.g. schizophrenia, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Alzheimer's disease, affective disorders]… the neurocognitive deficits, which are well-described clinical features of these disorders may be remediated by nicotine administration or smoking'. This notion is not limited to those with a formal psychiatric diagnosis, as it has been suggested that many 'normal' smokers may also be self-medicating their neurocognitive or other psychobiological abilities (Dinn et al. 2004).

In their review, Sacco et al. (2005) concluded that there was little empirical support for the self-medication model in normal smokers, whereas there was support in certain psychopathological disorders (Alzheimer's disease, ADHD and schizophrenia), although not in others (affective disorders). Newhouse et al. (2004) similarly concluded that nicotine could be advantageous for the neurocognitive deficits in schizophrenia, Alzheimer's disease, age-related mild cognitive impairment and ADHD. Fratiglioni and Wang (2000) commented that those suffering from Parkinson's disorder or Alzheimer's disease had a lower lifetime incidence of tobacco use and noted that cigarette smoking might have an 'undefined biologic neuroprotective influence'. Although in a prospective study into Parkinson's disorder, Alves et al. (2005) found that tobacco smoking did not confer any protection against cognitive decline and other aspects of disease progression. Turning to cognition in non-clinical smokers, Newhouse et al. (2004) noted: 'In contrast to studies in pathological states, studies of nicotine in normal nonsmokers tend to show deleterious effects'. Amongst a sample of 138 normal students, Dinn et al. (2004) found no empirical support for the self-medication model amongst the 23 regular smokers, although they did conclude that orbitofrontal deficits (as evidenced by disinhibited and impulsive behaviours) could be ameliorated by nicotine.

Newhouse et al. (2004) proposed that the reason for why certain psychopathological groups showed positive effects, was their lower baseline neurocognitive state. Normal smokers were seen as functioning at near-optimal levels already, whereas in neuropsychiatric disorders characterised by suboptimal cognition, performance improvements were then possible. This model was based on the Yerkes–Dodson inverted U function, which has been used to explain some aspects of performance modulation in normal smokers (Parrott 1992; Parrott and Craig 1992). Another potentially important factor is the greater intensity of cigarette use by psychopathological smokers. Neurocognitive gains have been demonstrated in normal smokers who follow a pattern of intensive 'chain' smoking (>60 cigarettes/day), possibly because they maintain constantly high levels of plasma nicotine throughout the day (Brown 1973; cited in Parrott et al. 2004). In a similar way, the very intensive smoking of some psychopathological groups may help them to engender relative psychobiological gains through high and/or never-falling plasma nicotine levels.

However, before it can be concluded that nicotine can be beneficial in certain psychopathological disorders, some limitations of the self-medication database need to be debated. Firstly the empirical evidence is quite variable, with psychobiological gains, no changes, and decrements, having all been demonstrated (Table 3 in Sacco et al. 2005). Many factors may underlie this variation. One important methodological confound is the different clinical–psychobiological profiles of those who decide to take up smoking, in comparison with those who do not. With reference to schizophrenia for instance, cigarette use is more prevalent amongst paranoid than non-paranoid sub-types (Beratis et al. 2001: Combs and Advokat 2000). Yet paranoid schizophrenia is typified by a hyperalert attentional style, whereas non-paranoid schizophrenia is characterised by hypo-

attentional styles, with minimal perceptual scanning and lower levels of socioenvironmental engagement (McGhie 1970). Hence, any differences in attentional test performance between smoker and non-smoker sub-groups, may well be a function of the underlying clinical condition, rather than of nicotine-use per se. This self-selection factor makes all cross-sectional comparisons problematic, whether in clinical and non-clinical populations, as genetic, intellectual, personality, and other factors may influence cognitive performance and mood state. It emphasises the necessity for long-term prospective research. To demonstrate the psychobiological consequences of nicotine-use in clinical subgroups, the same individuals should be followed over time, from before their take up of smoking. Such long-term studies have been crucial in demonstrating the deleterious effects of cigarette smoking in normal adolescent smokers (see earlier). They are also needed to assess the self-medication model in psychiatric and other clinical subgroups (see: Alves et al. 2005, summarised above). Such studies may need to be cover quite long time spans. Covey et al. (1997) found that 3 months after smoking cessation, 30% of those with a history of recurrent major depression prospectively experienced another major depressive episode. This may be interpreted as empirical support for the self-medication model, although it could be indicative of a more severe withdrawal syndrome. Indeed psychiatric patients and other heavy smokers with severe dependency may need to be assessed over a far longer time period, because they may be affected by a more severe and enduring withdrawal syndrome. If they were to be assessed over a couple of years, along with two control groups of continuing smokers and non-smokers (all with clinical depression), any change in the incidence of depressive episodes would provide a strong empirical comparison of the self-medication and deprivation-reversal models. Even with this powerful prospective design, multiple interpretations could still be possible because each group would be self-selected.

Another complicating issue is nicotine's aversiveness in some non-smokers, as selective drop outs may lead to adversely affect the emergent findings. The following citations come from two studies, which were published after the reviews by Newhouse et al. (2004) and Sacco et al. (2005). Lemay et al. (2004) investigated transdermal nicotine in 22 non-smoking Parkinson's Disorder patients, but 13 (59%) withdrew from the study 'mostly because of acute side effects' (note: with the remaining nine, the nicotine patch had no cognitive effects). Potter and Newhouse (2004) investigated transdermal nicotine in non-smoking adolescents with ADHD. Five participants were given the patch for 60 min, which led to significantly faster stop signal recognition, leading to the conclusion that nicotine can be cognitively beneficial. Yet their first three subjects has been given the patch for 90 min, but suffered acute side effects, so their findings were excluded. Perhaps the main problem with the model is the fluctuating levels of plasma nicotine induced by cigarette smoking. Self-medication via tobacco smoking is always likely to prove difficult, because the psychobiological states induced by the drug will also be fluctuating. Mood lability is at the core of nicotine dependency in cigarette smokers. So that even in those who may gain some neurocognitive advantages with nicotine, these are likely to be accompanied by mood vacillation and the constant need to forestall abstinence symptoms. Psychological lability may also affect cognitive and/or psychomotor task performance. This has rarely been studied, although Heffernan et al. (2005) noted that the worse 'everyday memory ability' of tobacco smokers, might be a reflection of fluctuating nicotine levels during storage and retrieval. Ashton et al. (1972) noted performance lability in an investigation of car driving and other cognitive skills. On the simple cognitive tasks there were no differences between the smokers and non-smoker controls. Whilst in the car driving simulator, overall foot-break reaction times did not differ between groups. However, the active smokers did display significantly greater variance in their performance: 'reaction times to light signals differed significantly from those of non-smokers, some being longer and some shorter'. It would be interesting to repeat this classic study, comparing active smoking with a steady-state delivery system such as transdermal nicotine. Its smoother pharmacokinetic profile should also make it a better-tolerated delivery system for any medicinal uses (although see above).

Some parallels with other psychosocial drugs

The subjective mood effects of all psychosocial drugs are broadly positive in short-term. Alcohol, amphetamine, cannabis, cocaine, Ecstasy/MDMA and opiates each produce acute effects that are subjectively pleasing. Cocaine induces an acute stimulatory 'rush', amphetamine produces an arousing 'hit', MDMA creates feelings of euphoria, heroin engenders soporific pleasures, alcohol disinhibits many behaviours and cannabis fosters geniality. Although not every acute drug effect is desirable, if they did not display a broadly positive profile, then they would not be used for recreational purposes (see Chapter 15 in Parrott et al. 2004). If explanatory models for these other drugs predominantly focused on their acute effects, then it might readily be concluded that they were psychobiologically useful. The main neuropsychobiological problems with psychoactive drug use generally emerge in longer-term studies. Only then do many of the drug-related problems become more apparent, with dependency and tolerance being crucial for understanding why so many psychoactive drugs become problematic. This same pattern also applies to nicotine (Parrott 1999, 2003; Parrott et al. 2004). Finally, the negative resource model outlined here is similar to that described by Baker et al. (2004) in their 'reformulation' of the negative reinforcement model for all forms drug dependency. They suggested that 'escape and avoidance of negative affect is the pre-potent motive for addictive drug use', including nicotine.

One key to understanding the psychobiology of nicotine may therefore be the abstinence–withdrawal syndrome. It is crucial for understanding the effects of acute nicotine reinstatement, as in daily cigarette smoking, and the longer-term psychobiological aspects of nicotine in regular

smokers. Genetic linkages have been established between nicotine dependency, personality factors such as neuroticism and various psychiatric predisposition factors (e.g. for depression, anxiety and ADHD). Many authors have debated the underlying nature of these links (e.g. Sullivan and Kendler 1999). One possibility is that they reflect a core dimension of withdrawal severity, and hence of liability to dependency. Indeed, genetic linkages between withdrawal severity and some of these other factors have been empirically demonstrated. Xian et al (2005) undertook a genetic study of 4,000 twins and found significant associations between the severity of nicotine withdrawal symptoms and various psychiatric and genetic markers. 'The strong association between psychiatric disorders and withdrawal severity and the significant genetic correlation between withdrawal and cessation highlight the importance of withdrawal severity'. Uhl (2004) also noted the utility of association-based genome scans for identifying vulnerability to both nicotine and many other psychoactive drugs. This raises the intriguing notion that mood vacillation with nicotine may be paralleled by mood vacillation under other psychoactive drugs, possibly via common underlying mechanisms. This could help explain certain psychobiological aspects of poly-drug use. For instance, different patterns of nicotine use and nicotine withdrawal have been demonstrated in smokers who are also recreational Ecstasy/MDMA users, and this may illustrate aspects of co-drug dependency (Parrott et al. 2005). Returning to the genetic aspects of smoking, this literature has emphasised the complex multi-factorial nature of the genetic influences and the variation in smoking phenotypes (Johnson et al. 2004; Sullivan and Kendler 1999; Xian et al. 2005; also Furberg et al. 2005). However, it should be noted that most genetic studies have used positive resource models for their phenotypic descriptions (e.g. Maskos et al. 2005); future genetic studies would benefit from focusing more on the negative resource aspects of nicotine. In conclusion, for a complete understating of the neuropsychobiology of cocaine, Ecstasy/MDMA or alcohol, both acute and chronic effects need to be considered. This same message holds for nicotine. It is only when the acute dose findings are complemented by long-term findings that a more complete picture of the psychobiology of nicotine can emerge.

Table 1 Some topics for future research

Mood vaccilation. Future studies should investigate mood vacillation rather than just mood states. How does mood vacillation relate to the development of nicotine dependency? Why do some smokers develop marked mood vacillation, whereas others manage to remain light/occasional smokers with minimal experience of mood change?
Cognitive vaccilation. Future studies might also focus on changes in cognitive skill. Simple attentional/working memory tasks with demonstrated sensitivity to nicotine (e.g. rapid visual information processing) would be ideal for monitoring subtle daily fluctuations in cognitive skill. As with mood states, marked individual differences are predicted. Many other aspects of neuropsychobiological vacillation could be also assessed.
Disadvantaged smokers. How does the initial baseline state relate to subsequent mood–cognitive–psychobiological modulation? Do neurotic pre-smokers develop the strongest stress fluctuation when they become regular smokers? Does this underlie their development of stronger nicotine dependency and, hence, lead to greater daily stress? Similarly, does pre-morbid depression predict greater smoking-related impairments in depressive states? The same is true with many other pre-dispositional characteristics, for instance attentional-cognitive vacillation in ADHD.
Initiation and cessation. Is there a relationship between the patterns of mood fluctuation during smoking, the mood control problems that develop during short-term abstinence, and the mood changes found during long-term cessation? How are they related to the early development of mood changes during tobacco initiation?
Genetic aspects. What are the genetic components to these various aspects of psychobiological vacillation? Are there specific aspects, which relate to different phenotypes of smokers? Are there broader core aspects, which contribute to a general vulnerability to nicotine use and other forms of drug dependency?

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