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# Gene-Environment Interplay in Affect and Dementia: Emotional Modulation of Cognitive Expression in Personal Outcomes

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**A multitude of factors, that either singly, interactively, or sequentially influence the gene-environment interplay in affective and dementia states, include several phases of neurodevelopmental liability in both humans and laboratory animals. Genetic vulnerability for both affective disorders and dementia describes a scenario distinguished by progressive need for concern, particularly in view of the interplay between these areas of ill-health. The contribution of emotional and cognitive expression to personal outcomes, e.g., as a function of affective personality type, a state-dependent analysis of personality characteristics, appears to pervade both the individual's experience of social and physical environments and the performance of cognitive tasks. The role of the endocannabinoids in mental health may offer insights for the psychopharmacology of both cognition and affect. Maladaptive emotional reactions and a defective cognitive ability will contribution to unsatisfactory/maladaptive coping strategies, in turn, leading to further complications of an affective and dysfunctional nature, eventually with a clinical psychopathological outcome. These considerations impinge upon critical issues concerning predisposition and vulnerability. Classical eye-blink conditioning provides a highly established procedure for assessment of defective physiology in models of Alzheimer's dementia. In order to develop a consideration of the array of situations presenting the variation of outcome due to type of affective personality, the role of fear and anxiety and stress in affective states influencing cognition are examined and the critical role of brain circuits mediating emotions influencing cognitive outcomes is discussed.**

*Keywords:* Gene-environment; Affect; Dementia; Emotion; Personality; Cognition; Eye-blink donditioning; Fear conditioning; Endocannabinoids; Stress; Anxiety; Depression; Vulnerability

## INTRODUCTION

Affect refers to feelings or emotions, and in a very real sense these feelings and emotions represent the outcome of an individual's evaluations/appraisals of the events impinging upon that individual throughout his/her existence. The outcome of these assessments may take various forms, some of which may give an impression of normality or others that of disturbance. In consequence, one may say then that the affective disorders are characterised by disordered feelings. There are some indications that disorders of affect may be heritable (*cf.* Moldin *et al.*, 1991). For example, close relatives of individuals afflicted with affective psychosis are ten times as likely to develop the disorder as other individuals (Rosenthal, 1971). The rate of concordance between monozygotic twins for an affective disorder was 69% whereas that for dizygotic twins it was 13% (Gershon *et al.*, 1976). The concordance rate for monozygotic twins was maintained whether or not the twins were raised apart. At gene level a pattern may be emerging. For example, a single dominant gene may underlie vulnerability for bipolar disorder (Spence *et al.*, 1995). In this regard, although it was suggested first that this gene be located on chromosome 11 (but see Egeland *et al.*, 1987; Kelsoe *et al.*, 1989), recent implications point to the "bipolar gene" possible location on chromosome 4, 5, 18, or 21 or the X chromosome (MacKinnon *et al.*, 1997; Berrettini, 1998; Garner *et al.*, 2001). On the other hand, multiple

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avenues of information regarding psychiatric illness resulting from traumatic/moderate psychosocial stressors that cause neurochemical perturbations, lasting from a few hours to several years, during critical/less critical periods of neurodevelopment are becoming available (Cameron *et al.*, 1998; Bergquist and Ekman, 2001; Cirulli, 2001).

At a most basic level dementia presupposes failure or disorder of cognition whereas disease states involving affect presuppose failure or disorder of emotion. Thus, the present papers pertaining to dementia and affect, in many aspects involving dysfunctionally-related substrates (Issa *et al.*, 1990; Lupien *et al.*, 1994; 1997; 1998), offer both the possibility of examining the brain systems involved in cognition and emotion and certain aspects of the highly personal outcome of each individual's particular 'configuration of cognitive and emotional characteristics', *i.e.*, the final outflow of expressions in behaviours, thoughts and dispositions that contribute to the product of an equation referred to, for present purposes, as personality. This 'configuration of cognitive and emotional characteristics' will result from the equation of genetic architecture as it progresses through the inconstancy of prenatal, postnatal and later development (Levine and Lewis, 1959; Joffe, 1965; Peacock *et al.*, 1995).

## COGNITIVE AND EMOTIONAL PROFILES DETERMINING AFFECTIVE PERSONALITY EXPRESSION

An individual's particular response to a negative event is dependent upon a profile consisting of the sum total of a complex array of characteristics, including intellectual and cognitive abilities, emotional 'make-up' as reflected by the relation between positive and negative affect, originality and flexibility in problem-solving, willingness to take personal risks. Through this notion, an individual's experience of stress is highly subjective, and coping behaviours may be perceived as homeostatic/transformation responses leading to either positive/negative outcome (Aldwin, 1994). Depressive or anxious predispositions are likely to affect the outcome of personal trait measurements (e.g., Hirschfeld *et al.*, 1983; Lauer *et al.*, 1997). Thus, two basic factors, labelled Positive Affect (PA) and Negative Affect (NA), identified in both intra- and inter-individual analyse across several variables including language and culture, have emerged as important dimensions of an individual's emotional experience (Zevon and Tellegen, 1982; Watson and Tellegen, 1985; Almagor and Ben-Porath, 1989; Meyer and Shack, 1989). These estimations of affect, through evoking responses pertaining to mood, bear strong relations to measures of personality and emotionality. Watson and Clark (Watson *et al.*, 1987; 1988a,b) showed that NA correlated substantially with measures of neuroticism/negative emotionality but was unrelated to measures of extraversion/positive emotionality (according to scales developed by Eysenck and Eysenck, 1975), whereas PA correlated substantially with measures of extraversion/positive emotionality but not with measures of neuroticism/negative emotionality.

In general terms concerning health and well-being, negative affect is associated with strong symptoms of stress (Watson and Clark, 1984; Watson *et al.*, 1988a,b), whereas positive affect presumes both a satisfactory control and perception of stressful events (Park *et al.*, 1996). Both NA and PA influence the extent to which an individual experiences and approaches stressful situations (Melvin and Molly, 2000). In contrast to NA, PA consists of enthusiasm, activity, control, commitment, alertness and challenge, and is associated generally with an individual's disposition to maintain a positive outlook over both time and circumstance (Watson *et al.*, 1987). It has been indicated (Wilson *et al.*, 1998) that there exist no significant correlations between the PA and NA scales of PANAS under normal conditions. Consequently, Norlander *et al.* (2002) presented the possibility of deriving high and low PA- and NA-values by individuals such that the scales could be combined in a model that offered four affective personality types: (a) individuals presenting high PA with low NA ("Self-actualisation"), (b) individuals presenting high PA with high NA ("High affective"), (c) individuals presenting low PA with low NA ("Low affective") and (d) individuals presenting low PA with high NA ("Self-destructive"). Thus, it was found that Self-actualizing individuals showed the best performance under stress whereas High affective individuals showed the lowest levels of systolic blood pressure during resting. No differences in performance during stress (Stroop test) were evidenced between younger and older participants encompassed by high positive affect whereas an age difference was obtained for high negative affect individuals (Norlander *et al.*, 2002). In subsequent studies it was found that the Self-actualizing individuals presented a more psychologically healthy profile, with regard to both stress and dispositional optimism than the Self-destructive individuals (Bood *et al.*, 2004).

The present review describes the results obtained from four different studies undertaken to investigate the influence of affective personality, as assessed by

application of the PANAS instrument, upon several different aspects of behaviour including subjective stress, perfectionism, dispositional optimism, substance use, relationship between energy and stress, anxiety and depression, partner relationships and coping strategies. In all four studies, five variables were a constant feature: subjective stress-psychological and - somatic, dispositional optimism, anxiety and depression.

**Participants in each of the four studies (I-IV)**

**Study I**: Seventy-three individuals (41 male and 32 female), of whom 40 were employed in different construction and metal work or nursing and health care positions (in Göteborg, Sweden) and 33 were university students (University of Göteborg, Sweden), participated. The mean age of the Student group of participants was 25.30 years (*SD* = 4.45) whereas the mean age of the Worker group, the men employed in construction and metal work and the women in nursing, was 38.35 years (*SD* = 11.38). The mean value for PA was 34.57 (*SD* = 6.93) and for NA was NA 21.64 (*SD* = 7.14).

**Study II**: Ninety-one individuals (26 male and 65 female), all of whom were high-school students (Vägga High School, Karlshamn, Sweden), participated. The mean age of these students was 17.40 years (*SD* = 1.02). They were derived from several different educational programmes, including 'Children and leisure activity' (*n* = 52), 'Humanities' (*n* = 9), 'Pure science' (*n* = 6), 'Social sciences' (*n* = 21), 'Nursing and Health care' (*n* = 3), and distributed chronologically as follows: 1st year: *n* = 19, 2nd year: *n* = 44, 3rd year: *n* = 28. As for Study I, the assessment of PA and NA, through application of the PANAS-test, was central to the purpose of the study. The mean value for PA was 33.33 (*SD* = 7.23) and for NA was NA 22.29 (*SD* = 7.73).

**Study III**: One hundred and thirty-nine individuals (95 male and 44 female employed in seven different occupational categories representing police, salesman, teachers, construction workers, physiotherapists, and office workers) participated. As for Study I, the assessment of PA and NA, through application of the PANAS-test, was central to the purpose of the study. The mean value for PA was 34.63 (*SD* = 6.83) and for NA was NA 20.91 (*SD* = 6.63).

**Study IV**: One hundred and seventy individuals (58 male and 112 female), all of whom were students at the University of Göteborg (Göteborg. Sweden), from the Faculties of Humanities and Social Sciences studying political sciences, sociology, languages and economics. As for Study I, the assessment of PA and NA, through application of the PANAS-test, was central to the purpose of the study. The mean value for PA was 34.96 (*SD* = 6.88) and for NA was NA 20.27 (*SD* = 6.97).

**Study V**: One hundred and ninety-six individuals (78 male and 118 female), all of whom were students at the University of Växjö (Växjö, Sweden), from the Faculties of Humanities and Social Sciences studying political sciences, sociology, languages and economics. As for Study I, the assessment of PA and NA, through application of the PANAS-test, was central to the purpose of the study. The mean value for PA was 35.21 (*SD* = 7.16) and for NA was NA 19.65 (*SD* = 6.67).

Anonymity was preserved throughout. The assessment of PA and NA, through application of the PANAS-test (Watson *et al.*, 1988b), was central to the purpose of the study. These values may be compared with the cumulative Swedish Norm group for those occupationally employed (*N* = 1010; PA: M = 34.80, *SD* = 6.51; NA: M = 18.48, *SD* = 6.36) that is currently under development and assessment (Norlander *et al.*, 2004). One-samples *t*-test did not show any significant difference between the PA-values or the NA-values of the present study and the norm group (*p* values > 0.6).

**Design**

The two dependent variables were Affective Personality (consisting of four personality types: Self-destructive, Low affective, High Affective and Self-actualization) and Group (Students and Workers). The four affective personality types were derived from the PANAS-test (Watson *et al.*, 1988b) through the application of a special procedure developed by Norlander *et al.* (2002). From this procedure, in Study I for example, one group was obtained that consisted of 18 participants (16 Students and 2 Workers) presenting a "self-destructive" personality, one group of 19 participants (7 Students and 12 Workers) presenting a "low affective" personality, one group of 19 participants (6 Students and 13 Workers) presenting a "high affective" personality and finally one group of 19 participants (4 Students and 13 Workers) presenting a "self-actualization" personality. The 40 workers/nurses and 33 university students provided the second dependent variable. The dependent variables of the present studies I-IV were derived from several different tests of subjective stress, dispositional optimism, and Hospital depression and anxiety, that were common to all four studies.

**Instruments**

***PANAS - Positive Affect and Negative Affect Scales***

The PANAS-instrument (Watson *et al.*, 1988b; Kercher, 1992; Varg, 1997) assesses the degree of

affect, both negative (NA) and positive (PA). The instrument consists of 10 adjectives for the NA-dimension and 10 adjectives for the PA-dimension. In the test manual (Watson *et al.*, 1988b), it is postulated that the adjectives describe feelings and mood. The participants were asked to estimate how they had been feeling during the latest period. Response alternatives are presented on 5-degree scales ranging from 0 = "not at all" to 5 = "very much". The responses to the negative adjectives were summated to a NA-result and the responses to the positive adjectives were summated to a PA-result. The PANAS-scale has been validated through studies focused upon several different routinely applied scales within psychopathology (Huebner and Dew, 1995). Wilson *et al.* (1998) have shown that there does not exist any significant correlation between the positive and negative affect, which is considered as an indication of divergent validity. Norlander *et al.* (2002) have developed the instrument further through the derivation of four types of personality. This procedure was implemented by dividing the result on the PA-scale into two equal parts thereby distributing the participants into one group with high PA and another group with low PA. The same procedure was implemented for participant responses on the NA-scale. Following this, the results from these two scales were combined through distributing the participants into four groups: high PA and low NA ("self-actualization"), high PA and high NA ("high affective"), low PA and low NA ("low affective"), and finally low PA and high NA ("self-destructive"). An identical procedure was maintained in the present studies described here.

***Background and Health Assessment***

The instrument is derived to provide background and health information about the participants. Items 1-16 dealt with each participant's current health status, status of personal relationships, alcohol, smoking, exercise habits, etc. - as well as intake of medicines affecting mood or pain. None of the studies indicated significant background/health assessment effects due to affective personality, with the exception of medicines affecting mood or pain. In this regard, a degree of caution is warranted until further health aspects of affective personality are assessed.

***Hospital Anxiety and Depression Scales (HAD)***

The instrument is derived to measure depressive and anxiety symptoms (Zigmond and Smith, 1983; Herrmann, 1997). It consists of 14 statements to which participants respond by marking one of either three or four response alternatives. For example, "I can sit still and feel relaxed" with response alternatives: Definitely, Generally, Seldom, Never, or, "Everything feels heavy" with response alternatives: Almost always, Often, Sometimes, Never, or, "I look forward with gladness towards this and that" with response alternatives: As much as before, Less than before, Hardly ever. Half of the statements were constructed to illustrate depressive symptoms whereas the other half to illustrate anxiety-related symptoms. Participants' responses thereby provided two final results, one pertaining to depressive symptoms, the other to symptoms of anxiety.

***Subjective Stress Experience (SSE)***

The instrument is derived from a diagnostic manual designed to assess different reactions to stress (Lopez-Ibor, 2002). Participants were required to estimate the extent to which different statements concurred with how they felt on an ordinary working/college day. The first part of the instrument consisted of 23 statements wherein participants were required to respond to the extent to which they experienced, for example, "Nausea or abdominal pain", or, "Overreaction to inconsequential inner stimuli/easily frightened", or, "Muscle tension", or "Sleep problems caused by worry". The test contained statements concerning symptoms implicating autonomic activation, mood changes, tension as well as other nonspecific symptoms associated with stress responses. Participants' estimations were carried out using a Visual analogue scale (VAS) whereby they marked a cross on a 10-cm line (1 at one end and 10 at the other) whereby 1 = "do not agree at all" and 10 = "agree completely". The results of the test provided a total estimation for somatic stress and one for psychological stress.

***Life Orientation Test (LOT)***

The test (Scheier and Carver, 1985) was constructed originally to study the extent to which the personality trait optimism was associated with the ability to develop suitable 'coping strategies' in connection with severe psychological and physical handicaps, e.g., tinnitus. Since the test has been shown to be successful for predicting successful coping strategies for soccer referees (Folkesson *et al.*, 2002), it was considered both sufficient and necessary for the present examination of affective personality type and subjective stress. LOT presents eight items, plus four filler items. The task for each respondent is to decide whether one agrees with each of the items described, on a scale anchored by 0: strongly disagree and 4: strongly agree. The test measures dispositional optimism, defined in terms of generalized outcome expectancies. According to Scheier and

Carver (1985), LOT offers a suitably scientifically prepared test with an estimated internal consistency of 0.76 (Cronbach's alpha) and a test-retest reliability of 0.79 (Pearson *r*). The test requires only five minutes for participants to complete.

As evident from Table 1, affective personality type is highly predictive of an individual's health: individuals with the 'self-destructive' type of affective personality invariably presented more psychological and somatic stress, more anxiety and depression and less disposi-

Table I Self-estimations (means ± SDs) of subjective stress, psychological and somatic, dispositional optimism, and Hospital anxiety and depression, by Self-actualization, High affective, Low affective and Self-destructive groups in Studies I-V.

| Affective personality | Self-actualisation | High affective | Low affective | Self-destructive |
|---|---|---|---|---|
| | | | | |
| **Subjective stress** | | | | |
| **Psychological I** | 15.06 ± 5.55 | 26.68 ± 16.66* | 18.15 ± 7.08 | 32.66 ± 12.11* |
| **Psychological II** | 23.84 ± 8.47 | 34.00 ± 13.45 | 26.42 ± 15.05 | 41.39 ± 19.58* |
| **Psychological III** | 14.54 ± 4.77 | 28.79 ± 14.81* | 17.10 ± 5.15• | 31.70 ± 14.34* |
| **Psychological IV** | 19.93 ± 7.88 | 29.96 ± 17.03* | 22.63 ± 12.11 | 39.16 ± 19.32* |
| **Psychological V** | 15.25 ± 7.57 | 24.42 ± 16.20 | 15.22 ± 7.95• | 25.94 ± 16.40* |
| | | | | |
| **Somatic I** | 21.00 ± 7.01 | 30.00 ± 14.41 | 28.42 ± 12.43 | 36.83 ± 13.74* |
| **Somatic II** | 31.00 ± 9.55 | 42.96 ± 18.91 | 35.00 ± 20.66 | 52.03 ± 27.08* |
| **Somatic III** | 15.28 ± 6.09 | 23.06 ± 11.22* | 16.27 ± 4.66• | 27.19 ± 13.75* |
| **Somatic IV** | 17.48 ± 6.51 | 28.57 ± 19.39*,$^{0}$ | 17.34 ± 9.02 | 25.14 ± 16.45*,$^{0}$ |
| **Somatic V** | 17.30 ± 9.76 | 24.09 ± 13.75 | 16.20 ± 9.92 | 24.31 ± 17.36 |
| | | | | |
| **Dispositional optimism** | | | | |
| **LOT I** | 24.00 ± 5.95 | 20.57 ± 6.71• | 22.00 ± 4.06• | 15.44 ± 4.92* |
| **LOT II** | 25.67 ± 7.09 | 21.07 ± 7.35• | 22.43 ± 5.39• | 16.12 ± 3.88* |
| **LOT III** | 24.12 ± 3.06 | 21.78 ± 5.24• | 22.96 ± 2.99• | 18.53 ± 4.02* |
| **LOT IV** | 23.47 ± 3.97 | 19.27 ± 4.15* | 19.76 ± 3.60* | 17.30 ± 5.28* |
| **LOT V** | 33.55 ± 6.14 | 27.90 ± 7.17 | 27.76 ± 6.67 | 24.94 ± 6.85* |
| | | | | |
| **HAD** | | | | |
| **Anxiety I** | 3.76 ± 3.03 | 6.63 ± 3.30*,• | 5.68 ± 2.49• | 11.00 ± 2.91* |
| **Anxiety II** | 4.48 ± 1.95 | 8.29 ± 3.75*,• | 5.54 ± 2.33• | 10.91 ± 3.43* |
| **Anxiety III** | 3.12 ± 2.06 | 7.74 ± 1.45* | 4.30 ± 1.92• | 8.28 ± 3.30* |
| **Anxiety IV** | 7. 43 ± 2.29 | 9.34 ± 2.80* | 8.38 ± 2.49 | 9.83 ± 2.93* |
| | | | | |
| **Depression I** | 1.94 ± 1.74 | 2.63 ± 2.43• | 2.79 ± 1.80• | 6.11 ± 2.74* |
| **Depression II** | 2.53 ± 1.81 | 3.42 ± 2.67 | 2.77 ± 1.83• | 6.43 ± 3.15* |
| **Depression III** | 1.74 ± 1.45 | 3.31 ± 1.99*,• | 2.59 ± 1.31• | 5.24 ± 2.89* |
| **Depression IV** | 4.58 ± 1.43 | 6.34 ± 1.83 | 7.45 ± 2.17* | 6.87 ± 1.95* |

*$p < 0.01$, *vs* self-actualisation group, Tukey HSD testing
•$p < 0.01$, *vs* self-destructive group, Tukey HSD testing
$^{0}p < 0.01$, *vs* low affective group, Tukey HSD testing
HAD = Hospital Anxiety and Depression
LOT = Dispositional optimism

tional optimism. Other studies (see FIG. 1) have demonstrated that these individuals present also markedly higher levels of perfectionism, higher experience of stress yet lower experience of energy, less effective coping behaviour, less positive aspects of personality on other 'trait-dependent' tests (e.g., Gordon's Personality Test), greater use of substances and medicines, more impulsivity, less 'thriving' and less satisfying sexual and partnership relations (unpublished manuscripts). The indices of positive/negative affect that form the basis of the four types of Affective personality: 'Self-actualisation', 'High affective', 'Low affective' and 'Self-destructive', appear not only to reflect the ongoing emotion state of individuals but to influence differentially the processing of information, judgements and decision-making processes (Schwarz, 2000). It has been suggested that positive emotions may lead to rather more cursory appraisals of the available information whereas negative emotions lead to zealous examinations (Hockey *et al.*, 2000). In the context of Affective personality type, one may thereby associate high positive affect scoring with an optimistic approach, and high negative affect scoring with a pessimistic approach, to cognitive performance; the present evidence reflects that the former generally provides a more satisfactory outcome (see FIG. 1).

Despite the lack of a proper understanding of conscious emotional experience and affective state, there are nevertheless several processes, coupled to discrete regions of the brain that warrant consideration as requirements for both the experiential and expressive components. It should be noted too that the greater part of research into emotions deals with fear and anxiety (*cf.* Blanchard *et al.*, 2001). These regional-functional processes include: the role of prefrontal cortex and anterior cingulate gyrus in working memory, the input of the amygdala into working memory, the mobilization of cortical arousal as a consequence of amygdala signalling, and the information bestowed by feedback signalling from various parts of the body (e.g., LeDoux, 1993; 1995). In both normal and conditions of disordered affect and dementia, the extent of functioning at each of these 'levels-of-processing' determines the final outcome, whether expressed as clinical depression, phobic anxiety, flatness-of-affect, loss of conscious memory, or even a 'self-destructive' personality.

## FEAR AND ANXIETY IN AFFECTIVE STATES INFLUENCING COGNITION

According to the notions of LeDoux (2003), the hippocampal system deals with the consolidation of explicit information, consciously encoded events, from associated cortical areas in a neutral fashion; this includes information pertaining to emotional content. Emotional information is processed by the amygdala and stored in associated subcortical, limbic regions. Note that this account needs to take into account the 'selective stimulus-processing' and 'response-selection' role of the anterior cingulate cortex; the anterior cingulate cognitive division plays a central role in attentional processing by: (1) modulating stimulus selection (*i.e.*, focusing attention), and/or (2) mediating response selection (Bush *et al.*, 1999). Consequently, effective working memory, the point of contact between implicit emotional and explicit fact knowledge, in frontal (and prefrontal) areas is a prerequisite for the conscious awareness of an 'emotionally-charged' situation. Nevertheless, much evidence has been accumulating over recent years by McGaugh and colleagues (*cf.* Cahill and McGaugh, 1996; Cahill *et al.*, 1996; Hatfield and McGaugh, 1999) implying a substantial role for the amygdala, and mobilizing a 'full-scale' HPA-axis involvement, in the storage of declarative conscious memories, using the basic inhibitory conditioning procedure (also used in the memory studies described below). By this notion, the amygdala modulates memory consolidation by influencing neuroplasticity in several parts of the brain: emotional experiences activate time-dependent cellular storage processes in different brain regions pertaining to the type of memory represented, as well as HPA activation of stress hormones and noradrenaline release in the basolateral amygdala which is the critical step for consolidation (McGaugh, 2000; Roozendaal *et al.*, 2001; McGaugh *et al.*, 2003).

Both fear and anxiety, as observed above, highly dependent on characteristics of affective personality (*cf.* Table I), are implicated in several types of affective state leading to clinical considerations (Nemiah, 1985; Leverich *et al.*, 2002; Myers and Davis, 2002; Kilic and Ulusoy, 2003). Much of the work that has emerged from LeDoux's laboratory hinges upon cellular mechanisms and brain circuitry involving fear memory formation/consolidation (Schafe *et al.*, 2000; 2001; Wilensky *et al.*, 2000; Bauer *et al.*, 2002; Lamprecht *et al.*, 2002) and reconsolidation (Debiec *et al.*, 2002). The plasticity to local and environmental stimulation in amygdala and hippocampal tissues was also established (Blair *et al.*, 2001; Yaniv *et al.*, 2001; Moita *et al.*, 2003). One avenue of clinical consideration has been the application of 'extinction-based' therapies through which the status of the fear-/anxiety-invoking conditioned stimulus is disrupted (Beckett, 2002;

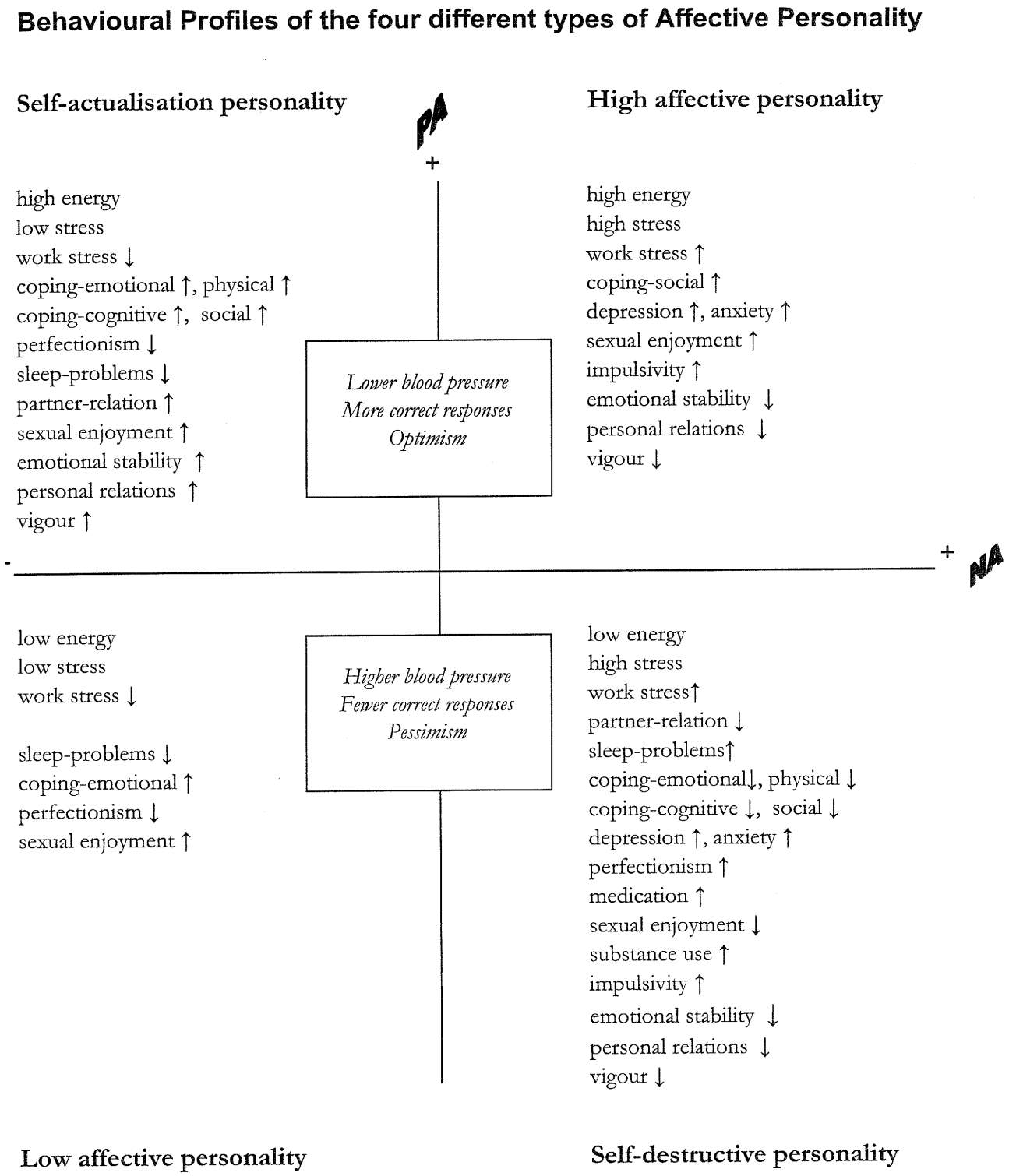


FIGURE 1 A summary of the emotional, behavioural, coping-ability and symptom profile associated with the four types of Affective personality comprising "Self-actualisation", "High affective", "Low affective" and "Self-destructive" individuals on the basis on their responses to the PANAS instrument, and as a possible predictor for eventual neuropsychiatric illness. The symbols: [arrow up/arrow down] indicate the following comparisons between Affective personality type:-
"Self-actualisation" group *vs* "Self-destructive" and "High affective" groups.
"Low affective" group *vs* "Self-destructive" group.
These profiles of the Affective personality types are derived from 20 different studies involving 1825 individuals presenting 'normal' health at the time of testing and includes high school students, university students, office workers, construction workers, factory workers, nurses, truck, taxi and bus drivers as well as university employees (*cf.* Andersson et al., unpublished data; Jansson *et al.*, unpublished data).
+ PA = High positive affect; + NA = High negative affect.

Rothbaum and Schwartz, 2002; Cammarota *et al.*, 2003; Paquette *et al.*, 2003). Izquierdo *et al.* (2004) have outlined the possible mechanisms (*cf.* Berman and Dudai, 2001) through which the inhibition of acquired fear may offer the amelioration of affective disorders by undermining the basic, and destructive, associations formed as the consequence of relatively simple classical Pavlovian conditioning (*cf.* Archer, 1982). Furthermore, in the context of memories for fear-provoking events, Izquierdo *et al.* (2004; but also Vianna *et al.*, 2001; 2003a,b; Szapiro *et al.*, 2003) and others (Falls *et al.*, 1992; Santini *et al.*, 2001; Davis, 2002; Walker *et al.*, 2002; Bahar *et al.*, 2003) have outlined the molecular basis of fear extinction in the amygdala and hippocampus, but nevertheless the involvement of prefrontal regions and other limbic areas is not to be neglected (e.g., Quirk *et al.*, 2000; Barros *et al.*, 2001; Milad and Quirk, 2002; Quirk, 2002). In addition, Igaz *et al.* (2004) have provided information pertaining to transcriptional response networks involved in memory formation. Applying the same one-trial inhibitory avoidance conditioning technique (*cf.* Izquierdo *et al.*, 2004), they obtained two temporal 'windows' of sensitivity to transcriptional and translational inhibitors infused into the hippocampus, at training time and 3-6 hours after. It was shown that these intervals were in complete synchronicity with the involvement of hippocampal cAMP/PKA (protein kinase A) signalling pathways in memory consolidation. Finally, once again utilizing the same one-trial, step-down inhibitory avoidance procedure in rats, Cammarota *et al.* (2004) have demonstrated that long-term memory consolidation was blocked by antagonists of the NMDA (*N*-methyl-D-aspartate) and AMPA [2-amino-3(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid] -receptors, infused into the CA1 region of the dorsal hippocampus, shortly after training. Their findings underline the interrelational role of NMDA and AMPA in the onset of activity-dependent impulses as prerequisite to the synaptic efficacy for the storage and later expression of new 'emotionally-based' memories, as would be expected from the earlier indications (Barria *et al.*, 1997; Cammarota *et al.*, 2000; Brun *et al.*, 2001).

The implications of cannabinoids in the regulation of anxiety-associated behaviours in both humans and animals have been documented (e.g., Navarro *et al.*, 1997; Rodriguez de Fonseca *et al.*, 1997; Robson, 2001). As described by Manzanares *et al.* (2004), the major distribution and density of the cannabinoid CB1 receptor in the brains of rats appears first and foremost in the cerebellum and substantia nigra pars reticulata, followed by the hippocampus, entopenduncular nucleus and globus pallidus, and markedly too in the regions of the frontal cortex and primary olfactory cortex and olfactory tubercle (Herkenham, 1991), areas associated with affective fluctuations. Thus, it is interesting to note the effects of the cannabinoid ligand, anandamide, upon the HPA-axis in rats (Weidenfeld *et al.*, 1994). Particularly in adolescents, adverse effects of cannabinoids affect emotional and personal characteristics (Fergusson and Horwood, 2000; McGee *et al.*, 2000; Johns, 2001). Certainly, taken in regard to the variations of Affective personality type, the involvement of this drug-receptor interaction with predisposing personality trait-characteristic may be of relevance (McKenna, 1997). Manzanares *et al.* (2004) discuss also the involvement of cannabinoid use in cannabis-induced anxiety (Grispoon and Bakalar, 1997), aggressive behaviour (Kouri *et al.*, 1999), depressive symptoms associated with use of cannabis (Bovasso, 2001; Degenhardt *et al.*, 2001; Thomas, 1993), and different aspects of cognitive deficits (Solowij, 1998; Hall, 2001; Solowij *et al.*, 2002). Finally, in connection with aspects of stress and affective personality, the interaction of drug use and stress expressions ought to be considered (e.g., Piazza and Le Moal, 1998).

Applications of electrophysiological methodologies for the assessment of cognitive performance (*cf.* Gruart *et al.*, 1995; 2000; Trigo *et al.*, 1999; Delgado and Gruart, 2002) have made possible the study of physiological processes in learning and memory through capturing the neurogenerative processes genetically-manipulated in transgenic and/or knockout mice (Selkoe, 2002; Vogel *et al.*, 2002). Delgado *et al.* (*cf.* Rodriguez-Moreno *et al.*, 2004) describe a series of studies using an "electrical shock/SHOCK" trace conditioning procedure in a learning task set-up that involves the hippocampus and cerebral cortex (Munera *et al.*, 2000; 2001). It was shown that these techniques were highly applicable for both the assessment of cognitive deficits in models mimicking AD conditions (e.g., Chen *et al.*, 2000; 2003), and the eventual therapeutic effects of drugs acting on cholinergic systems (Terry and Buccafusco, 2003; Trinh *et al.*, 2003; Rodriguez-Moreno *et al.*, 2004).

## STRESS IN AFFECTIVE STATES INFLUENCING COGNITION

Both measures of subjective stress, psychological and somatic (*cf.* Table I), showed marked and consistent associations with type of affective personality, and have been confirmed in several studies assessing

Energy-Stress as a function of each of the four types of affective personality. Thus, it may be observed that individuals included in the category "Self-destructive" personality expressed, typically, low energy but high stress, whereas individuals included in the category "Self-actualisation" personality expressed, typically and conversely, high energy and low stress. Individuals with "High affective" personality expressed both high levels of energy and stress whereas individuals with "Low affective" personality expressed both low energy and stress. It should be noted too that stress at work place was high in the Self-destructive and High affective personality types but low in the Self-actualisation and Low affective personality types (see FIG. 1). Tragically, individuals afflicted with the Self-destructive type of affective personality, however transiently, were found to have more sleep problems, greater perfectionism, more use of medication and substances, and yet lesser emotional, physical, cognitive and social coping, deteriorated partner relations and less sexual enjoyment, less emotional stability, worse personal relations and less vigour. Not least of it was shown that the Self-destructive type of affective personality performed worse under conditions of stress than the Self-actualisation type (Norlander *et al.*, 2002). By the above notions, psychopathological trends may derive from aspects of personality through several avenues (Akiskal *et al.*, 1983). Taken together, although these substantial disadvantages ought to provide a recipe for neuropsychiatric vulnerability, it is essential to consider that the influence of stress in the pathophysiology of psychiatric disease states (Szeszko *et al.*, 2003; Goldapple *et al.*, 2004) may vary considerably due to an individual's personal characteristics.

The close, and eventual causal, relations between neuropsychiatric vulnerability and personality through genetic links to major depressive illness and/or anxiety is described from different aspects in the recent paper by Fanous and Kendler (2004). As in the present case, the associations between personality types and depressive disorders appear compelling (*cf.* Kerr *et al.*, 1970; Wetzel *et al.*, 1980; Boyce *et al.*, 1991; Fanous *et al.*, 2002; Farmer *et al.*, 2002). Furthermore, these associations gather momentum when viewed from a perspective of genetic predisposition and covariation (Nyström and Lindegård, 1975; Jardine *et al.*, 1984; Maier *et al.*, 1992; Neuchterlein *et al.*, 2002), plausibly linked to serotonergic neurotransmission (Greenberg *et al.*, 2000; Melke *et al.*, 2001). Fanous and Kendler (2004) have opened several avenues for consideration of the contribution of a "Self-destructive" affective personality to eventual psychiatric disorder, albeit in the absence of established "susceptibility genes" for major depression; although most of the evidence they present remains indirect, as they put it (*cf.* family and twin studies), it is arguable that personality and the 'liability', whether neurodevelopmental or environmental, to psychiatric illness are influenced by variation in the same genes.

Among the various regions of the brain contributing to the sufficiency and necessity of an optimal level of cognitive performance under conditions of stress, the role of the prefrontal cortex and hippocampus is often cited, as rewiewed by Jay *et al.* (2004a; but see also Jay, 2004b). The hippocampus and prefrontal cortex, essential for effective functioning of executive and working memory processes (e.g., Floresco *et al.*, 1997), are regions highly sensitive to environmentally-instigated stress and/or affective ill-health (e.g., Sheline *et al.*, 1999; Mizoguchi *et al.*, 2000; Shakesby *et al.*, 2002; Vermetten and Bremner, 2002; Rocher *et al.*, 2004), and in this regard the involvement of the anterior cingulate cortex in the selection of relevant stress-associated stimuli ought not to be overlooked.

## INTERACTIVE EMOTIONAL-COGNITIVE EXPRESSION AND OUTCOME

The outcome of emotional-cognitive brain interactive processes has received much attention recently (Forgas, 1995; Bless, 2000; Fiedler, 2000; Clore *et al.*, 2001; Gasper, 2004). It has been suggested that the brain circuits underlying cognition and emotion may serve to produce a configuration consisting of four different processes: one of which would be automated (unconscious, implicit) and one of which would be controlled (conscious, explicit) whereas the remaining two would be interactive (Camerer *et al.*, 2004). Certain expressions of behaviour are activated by one or a couple of these processes but most behaviours consist of the involvement of all four processes. According to one notion (e.g., LeDoux, 1996), the neural connections stemming from the emotional circuitry to that of cognition is stronger than in the converse direction, which may prompt the conclusion that there is a tendency for emotions to guide cognitions. Some support of sorts may by offered by the case that individuals' minimal deficits of cognitive ability but marked deficits in emotional functioning demonstrated not only major problems in making decisions but when they eventually did so these were found to be the wrong ones (Bechara *et al.*, 2000). To some extent, measures of cerebral activity may provide reflections of an individual's current emotional 'set-up' (Damasio *et al.*,

2000). The contribution of emotional circuits under normal conditions is a requirement for satisfactory decision-making, taking the form of 'adaptively-suitable' affective judgement, and is in turn dependent on suitable 'somatic markers'. In this context, patients with bilateral damage to ventromedial areas of the prefrontal cortex (PFC) failed to demonstrate the emotional reactions normally associated with making decisions (Bechara, 2004). Furthermore, patients with right hemisphere PFC damage showed less sensitivity for the possible negative consequence of their decisions whereas those with left hemisphere damage were less sensitive to possible positive results.

Any consideration of interactive cognitive-emotional expression ought to gird itself with the texture of psychopathological vulnerability. Le Moal *et al.* (2004) used animal models to examine the influence of genetic background and environmental factors, that shape phenotypes, in showing the development of advantages consistent with inherent/acquired individual differences or by addressing the role of perinatal life events and stress. In adults, life events and environmental factors may transform a phenotype, permanently, even in inbred strains; the environment and genome interact to shape a given genome. As indicated, the dentate gyrus continues to produce neurons in the process so-called 'hippocampal neurogenesis', and as discussed above, the region is intimately involved with memory and subject to the deleterious effects of aging accompanied by decreased neurogenesis. Le Moal *et al.* (2004) show the existence of huge inter-individual differences for spatial memory performance in aged rats (20-month-olds): some of these perform as well as young adults, others are not able to acquire the task, whether in a radial arm maze or in a circular water maze. Thus, there was a clear correlation between spatial memory performance and cell proliferation, cell survival and with the rate of neurogenesis. The non-impaired aged rats (comparable performance to young adults) exhibited a higher number of new neurons than those impaired aged rats (Le Moal *et al.*, 2004). The authors present the relationship between an ongoing hypothalamic-pituitary-adrenal (stress) axis reactivity, hippocampal efficacy, propensity toward neurogenesis and memory performance, with reference to other animal models. Thus, prenatal stress induces permanent hyperactivation of the HPA stress axis (see also De Wied and Sigling, 2002; Levine, 2002; Van Praag, 2002). The prenatally stressed animals showed defective memory performance at 22 months of age, concurrent with marked decreases in new neuron survival and hippocampal neurogenesis. Conversely, adrenalectomized adult rats took on the prowess of the group of non-impaired 20-month-olds, incorporating a stimulated neurogenesis with functional performances comparable to the young adults. There appears to be an inherent neuronal program, neurogenesis, that may be manipulated and oriented in one or another phenotypical typology exemplifying long-term-induced vulnerability and a new allostatic state, emotional and stress systems modulating brain state alterations with the hippocampus as one of several regional targets.

## AFFECTIVE STATES IN DEMENTIA

Many of the behavioural features, apparently not related directly to cognition of dementia, pertain to the patient's affective state combined with an inability to express this state (Stokes, 1996; Woods, 2001), and may present a major constraint for treatment outcome (Donaldson *et al.*, 1998). Some degree of sensitivity to the emotional responses of the social environment is retained to a marked degree although cognitive (and often even the most basic abilities) are the major features in decline; this 'affective capacity' has tended to be overlooked in the focus upon cognitive and functional symptoms (O'Neill, 1997). Thus, the eventual co-morbidity of depressive state in dementia, or neurological disorder with dementia, remains an important issue (Aarsland *et al.*, 1996; Newman, 1999), particularly with regard to the probable parallel degeneration of several neuronal substrates (Palmer *et al.*, 1988). In addition, it was found that in patients with dementia of Alzheimer's type (AD) fear conditioning was impaired (Hamann *et al.*, 2002), implying some degree of procedural memory deficit pertaining to emotion memory. It is worth noting that amongst other areas of degeneration there are several regions of the medial temporal lobe that are compromised in AD patients. In this regard, Peper *et al.* (2001) found that patients with selective unilateral lesions to the amygadala-hippocampus (left or right hemisphere) failed to show an autonomic (electrodermal indicators) conditioning effect, compared with controls, to negative emotionally-charged facial expressions. Selective considerations of affective-cognitive relationships at regional sites that elucidate the overlying circuits may provide a greater impetus to an understanding of personal outcomes in stressful (aversive) situations (LeDoux and Gorman, 2001; LeDoux and Collingridge, 2002).

In view of the observation that emotional expression is largely intact in AD patients (Magai *et al.*, 1996), there appears an intimate association between emotional make-up in affective states and surviving cognitive

propensity in the demented individual, of relevance for treatment outcome, that need to be elaborated (Woods, 1999; James, 2001). It is possible too that affective reactivity may be adversely influenced by defective capacities for the processing of the emotionally-charged information available and several neurological conditions, including dementia, are associated with such deficits: patients with organic brain disease including AD, showed deficits in the recognition of facial expressions (Kurucz *et al.*, 1979), and deficits in emotion processing comprehension were obtained in patients with fronto-temporal dementia (Keane *et al.*, 2002), Huntington's disease and unilateral stroke (Speedie *et al.*, 1990), temporal lobectomy (Adolphs *et al.*, 2001) and Parkinson's disease (Breitenstein *et al.*, 2001). It has been found too that AD patients employed different processing strategies to healthy controls when studying facial photographic material, with greater focus upon 'off-face' aspects and less focus upon face and eye areas (Ogrocki *et al.*, 2000). Recently, Bucks and Radford (2004) observed that AD individuals had deficits in emotional processing ability compared with healthy older adult controls, but nevertheless, emotion-processing ability was preserved relative to general cognitive ability.

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