doi:10.1093/scan/nsn018 SCAN (2008) 3, 262–269

Hippocampal volume is positively associated with behavioural inhibition (BIS) in a large community-based sample of mid-life adults: the PATH through life study

Nicolas Cherbuin,[1] Tim D. Windsor,[1] Kaarin J. Anstey,[1] Jerome J. Maller,[2] Chantal Meslin,[1] and Perminder S. Sachdev[3,4]

[1]Centre for Mental Health Research, Australian National University, Canberra, Australia, [2]The Alfred & Monash University, Dept. of Psychological Medicine, Melbourne, Australia, [3]School of Psychiatry, University of New South Wales, Sydney, Australia, and [4]Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia

The fields of personality research and neuropsychology have developed with very little overlap. Gray and McNaughton were among the first to recognize that personality traits must have neurobiological correlates and developed models relating personality factors to brain structures. Of particular note was their description of associations between conditioning, inhibition and activation of behaviours, and specific neural structures such as the hippocampus, amygdala and the prefrontal cortex. The aim of this study was to determine whether personality constructs representing the behavioural inhibition and activation systems (BIS/BAS) were associated with volumetric measures of the hippocampus and amygdala in humans. Amygdalar and hippocampal volumes were measured in 430 brain scans of cognitively intact community-based volunteers. Linear associations between brain volumes and the BIS/BAS measures were assessed using multiple regression, controlling for age, sex, education, intracranial and total brain volume. Results showed that hippocampal volumes were positively associated with BIS sensitivity and to a lesser extent with BAS sensitivity. No association was found between amygdalar volume and either the BIS or BAS. These findings add support to the model of Gray and McNaughton, which proposes a role of the hippocampus in the regulation of defensive/approach behaviours and trait anxiety but suggest an absence of associations between amygdala volume and BIS/BAS measures.

Keywords: BIS; BAS; MRI; hippocampus; amygdala

INTRODUCTION

Personality research and neuropsychology have in the past followed largely parallel paths with little intersection between the two fields. Recently, it has been more widely recognized that being able to identify neural structures underlying personality traits would be of great benefit to testing the assumptions of personality theories, refining models of personality and assessing how personality measures can in conjunction with neuropsychological measures assist in predicting outcomes for cognitive functioning, health and well-being (Ozer and Benet-Martinez, 2006).

Received 25 July 2007; Accepted 11 June 2008
Advance Access publication 29 July 2008

The authors are grateful to Anthony Jorm, Helen Christensen, Bryan Rodgers, Wei Wen, National Capital Diagnostic Imaging group, Patricia Jacomb, Karen Maxwell, June Cullen the Neuroimaging Group, NPI, Prince of Wales Hospital and the path interviewers. N.C. is funded by Alzheimer's Australia Research and the Centre for Mental Health Research at the Australian National University. T.W. is funded by the National Health and Medical Research Council (NHMRC) grant No. 418020. K.A. is funded by NHMRC Research Fellowship No. 366756. The study was supported by NHMRC of Australia Unit Grant No. 973302, Program Grant No. 179805, NHMRC project grant No. 157125, grants from the Australian Rotary Health Research Fund and the Australian Brewers Foundation.

Correspondence should be addressed to Nicolas Cherbuin, Centre for Mental Health Research, Building 63, Australian National University, Canberra, ACT 0200, Australia. E-mail: nicolas.cherbuin@anu.edu.au.

Gray and McNaughton were among the first to systematically develop a model linking biological and neuropsychological structures to personality traits (Gray and McNaughton, 2003; McNaughton and Gray, 2000). Meticulous experiments conducted with rats showed that animals differently conditioned to fear or anxiety differed in their susceptibility to reward or punishment. Gray and McNaughton also showed that specific neural structures were likely to be involved in the modulation of fear/anxiety and other behaviours such as experimenting with novel stimuli, and that these behaviours could be related to conceptions of personality. Their model outlined three systems with the capacity to differentially affect behaviour: the behavioural inhibition system (BIS), the behavioural activation system (BAS) and the fight-flight system (FFS).

A number of alternative and revised models have been proposed, but in general models based on Gray and McNaughton's research suggest that the BIS responds to conditioned (and in the latest model, unconditioned) stimuli of punishment and non-reward, and leads to behavioural inhibition, heightened arousal, passive avoidance and is associated with anxiety. In contrast, the BAS responds to

conditioned (and in the latest model, unconditioned) stimuli of reward and non-punishment, promotes goal-directed behaviour and produces positive emotions while the FFS co-ordinates rapid response to immediate threats to survival (Gray and McNaughton, 2003).

Although the neural structures underlying behavioural activation and inhibition measures have been extensively studied in rodents, limited evidence is available to demonstrate such a relationship in humans. The following sections summarize evidence showing an association between behaviour, behavioural inhibition and activation tendencies and neuroanatomical structures in humans and suggests a possible association between BIS/BAS and hippocampal and amygdalar volumetric measures that will be tested in the present study.

Assessment of BIS/BAS tendencies

Much of the research concerned with BIS/BAS activity in humans has utilized the BIS/BAS scales developed by Carver and White (1994). These measures operationalize BIS/BAS sensitivities as reflecting relatively stable individual differences in tendencies toward approach and avoidance behaviour. In keeping with Gray and McNaughton's conceptualization, Carver and White's measure of BIS sensitivity reflects responsiveness to signals of negative outcomes, and tendencies to inhibit behaviour that may result in undesirable consequences. Three separate BAS subscales are aimed at capturing conceptually distinct elements of BAS sensitivity. The BAS-Drive (BAS-D) subscale reflects tendencies toward the dedicated pursuit of goals, while the BAS-Reward Responsiveness (BAS-RR) subscale represents degree of sensitivity to the occurrence or anticipation of reward. BAS-Fun Seeking (BAS-FS) reflects individual differences in the degree of impulsivity associated with approach behaviour.

The validity of Carver and White's scales is supported by studies showing an association between the BIS/BAS measures and genetic polymorphism (DRD2 & COMT) of the dopaminergic system thought to be involved in the brain's inhibition/reward system (Reuter *et al.*, 2006), neuroimaging findings showing an association between measures on the BIS/BAS questionnaire and activation of the amygdala (Cools *et al.*, 2005), and in studies of healthy and pathological samples demonstrating expected relationships between the BIS/BAS and other validated measures of personality (Campbell-Sills *et al.*, 2004). In addition, the BIS/BAS measures have been shown to be useful in predicting behaviour. For instance, individuals high on the BAS-RR scale have been shown to produce greater levels of activation in the brain appetitive centres (amygdala, midbrain, orbitofrontal and ventral pallidal regions) when presented with pictures of appetizing food (Beaver *et al.*, 2006) and to have a higher incidence of dysfunctional eating habits (Dawe and Loxton, 2004). Moreover, pain catastrophizing (the tendency to focus on pain and negatively evaluate one's ability to deal with pain) has been shown to be positively related to the BIS measure in adolescents (Muris *et al.*, 2007), while in adults, self-reported defensive measures from a threat scenario questionnaire was positively correlated with the BIS scale (Perkins and Corr, 2006).

Although Gray and McNaughton model of behavioural inhibition and activation was originally conceived independently of theories of personality, it has progressively been linked with these constructs and particularly Eysenck's conception of introversion–extraversion and neuroticism (Gray, 1981; Smillie *et al.*, 2006). Tests of these associations are beyond the scope of the present article but briefly, Gray suggested that by rotating Eysenck's axes of introversion–extraversion and neuroticism by 45°, these constructs should map well on individual susceptibility to signals of reward and susceptibility to signals of punishment predicting that the BAS should be composed of two parts: extraversion and one part neuroticism, while the BIS should be two parts: neuroticism and one part extraversion (Gray, 1970). However, these predictions have not always been supported by empirical investigation and might need to be adapted in future models (see Smillie *et al.*, 2006 for a review).

BIS/BAS NEUROANATOMICAL CORRELATES

The BIS and BAS neuroanatomical correlates are not yet well understood but are thought to involve the amygdala, septo-hippocampal system and the prefrontal cortex (BIS) and the amygdala, striatum and prefrontal cortex (BAS) as well as other structures (hypothalamus, cingulate and periaqueductal grey). The focus of the present study will be on the amygdala and the hippocampus, but in order to understand their role in a broader neuroanatomical context an overview of the functional involvement of the main structures contributing to the BIS and BAS will be discussed below.

In their latest model, Gray and McNaughton (2003; McNaughton, 2006) suggest that the septo-hippocampal system, in conjunction with the entorhinal cortex and the posterior cingulate, act as a control gate between currently active goals. When no conflict arises between these goals, no information is passed on for further processing and threat detection. However, when two or more goals conflict with each other (in terms of approach avoidance), the hippocampal system is thought to increase the valence of adverse outcomes associated with present goals, in a recursive manner, and to pass on this information to target structures (basal ganglia, frontal cortex, amygdala, hypothalamus) until one goal is sufficiently activated to take control of the motor mechanisms. The suggestion that increased hippocampal activity is associated with increased behavioural inhibition is supported by findings showing an association between BIS activity and increased hippocampal volume in young adults (Barros-Loscertales *et al.*, 2006a), an association between larger hippocampal volumes and increased anxiety

(Rusch *et al.*, 2001) and findings showing that impulsivity in human participants is associated with reduced hippocampal volumes (Zetzsche *et al.*, 2007). These findings also suggest an association between hippocampal volume and function.

Other findings in human have not supported a positive association between BIS and hippocampal volume, with one study showing that harm avoidance (which theoretically is a concept similar to the BIS) was associated with smaller regional brain volume in the left hippocampus (Yamasue *et al.*, 2008). Other studies in rats, produced conflicting results with increased anxiety being associated with increased or decreased hippocampal volumes depending on the manipulation conducted (Kalisch *et al.*, 2005); but it is not clear how experimental studies in rats relate to human neuropsychological control of behaviour.

The amygdala is thought to mediate simple (undirected/directed escape signals originating in the periaqueductal grey and medial hypothalamus) and complex (passive avoidance signals emanating from the hippocampal system) avoidance responses. Gray and McNaughton and others have shown in animal, pharmacological and functional imaging studies that the amygdala is essential for fear conditioning (Sigurdsson *et al.*, 2007), that its activity is modulated by anxiolytic drugs used to treat anxiety and depression, and that emotion processing (e.g. of faces), which is instrumental in determining whether an individual should be approached or avoided, produces greater levels of activity in the amygdala (Cools *et al.*, 2005). BIS activity has also been found to be associated with increased amygdalar volume in young adults (Barros-Loscertales *et al.*, 2006a). These results, as well as supporting an association between BIS and amygdala, suggest a possible association between greater activity and larger volume of this structure.

In association with the amygdala the anterior cingulate is believed to be involved in active danger avoidance. In contrast, the posterior cingulate appears to process information from the hippocampal system to deal with danger approach behaviour. In support of an association between cingulate cortex and behavioural inhibition, Gray *et al.* (2005) found that a higher BIS was associated with higher, task-related activation in the anterior cingulate cortex while performing a cognitive control task. The prefrontal cortex (as well as the cingulate cortex) interacts with the structures discussed above and is involved in danger avoidance and in planning actions rather than assessing goal conflicts *per se*. In addition, the striatum, and frontal cortices are thought to be involved in behavioural activation, thus interacting with the septo-hippocampal system to stimulate approach behaviours. The relationship between the striatum and the BAS has been demonstrated by Barros-Loscertales *et al.* (2006b) in a study showing that scores of the BAS-RR scale were negatively correlated with grey-matter density in the striatum in a voxel-based morphometry study.

Finally, measures of neuroticism and extraversion, which are thought to be related to behavioural activation and inhibition, were found to be correlated with cortical thickness in the prefrontal cortex, but not the amygdala, of healthy humans (Wright *et al.*, 2006). While in another study, individuals with higher bilateral cortical activity (measured by EEG) were found to score higher on a global BAS measure (Hewig *et al.*, 2006). Moreover, studies in patients with unilateral cortical damage have shown that lateralized lesions in the prefrontal cortex differentially affect mood with left-sided lesions being associated with a decreased capacity to experience positive affect (Davidson, 2001).

Current study

Although our understanding of the cerebral substrates of the BIS and BAS has progressed in recent times, a limited number of studies have been able to demonstrate a clear relationship between the BIS and the BAS and their underlying neural structures, and few have done so in non-clinical and/or large samples. The aim of this study was to investigate the relationship between volumetric measures of the hippocampus and amygdala and the BIS/BAS measures proposed by Carver and White (1994) in a large community-based cohort of middle-aged adults. It was predicted that higher measures on the BIS would be associated with larger amygdalar and larger hippocampal volumes since greater activation/volume of these structures have been shown to be associated with greater levels of anxiety. The nature of an association between BAS, amygdalar and hippocampal volume was more difficult to anticipate based on the contradictory evidence presented above. Consequently, we did not predict the direction of association between these variables but used the present study to explore this relationship.

Finally, since the BIS is conceptually, and physiologically according to Gray and McNaughton (2003), closely related to the experience of anxiety it was important to consider whether tendencies toward approach (BAS) and avoidance (BIS) behaviours might reflect the presence or absence of underlying mood disorders. Particularly, because the hippocampus and amygdala might be affected by the pathological processes associated with extreme anxiety and depression, although research to date has produced somewhat conflicting evidence (Rusch *et al.*, 2001; O'Brien *et al.*, 2004; Colla *et al.*, 2007; Konarski *et al.*, 2008). To examine the possible influence of psychopathology on the associations between BIS/BAS and hippocampal and amygdalar volumes, the associations were examined in the total sample, and in a sub-sample excluding participants reporting use of antidepressive medication.

METHODS

Participants

The sample was drawn from the PATH Through Life Project designed to study the risk and protective factors for normal ageing, dementia and other neuropsychiatric disorders (Maller *et al.*, 2006). This PATH Project cohort comprised 2530 individuals aged 44–48 years who were residents of the

city of Canberra and the adjacent town of Queanbeyan, Australia and were recruited randomly through the electoral roll. Enrolment to vote is compulsory for Australian citizens. A randomly selected subsample of 656 participants was offered an MRI scan, which 503 accepted, and 431 (85.7%) eventually completed. There were no differences in age, sex and years of education between those who had an MRI scan and those who did not ($P > 0.05$). One scan was lost due to a technical fault, giving a total number of 430 scans. The reasons for not undergoing an MRI scan after having initially agreed included subsequent withdrawal of consent, medical conditions contradicting MRI and claustrophobia or other anxiety about the procedure. Age, sex and years of education were recorded during the interview, among other variables. The study was approved by the ethics committees of the Australian National University, Canberra and the University of New South Wales, Sydney, Australia.

MRI acquisition

MRI data were acquired on a 1.5 Tesla Gyroscan scanner (ACS-NT, Philips Medical Systems, Best, The Netherlands). T1-weighted 3D structural MRI images were acquired in coronal plane using Fast Field Echo (FFE) sequence. About mid-way through this study, for reasons outside the researchers' control, the original scanner (Scanner A) was replaced with a similar Philips scanner (Scanner B). The scanning parameters were kept essentially the same. The first 164 subjects were scanned on Scanner A with TR = 8.84 ms, TE = 3.55 ms, a flip angle of 8°, matrix size = 256 × 256, slices 160 and the field of view (FOV) 256 × 256 mm^2. Slices were contiguous with slice thickness of 1.5 mm. For the remaining 268 subjects scanned on Scanner B, the TR = 8.93 ms, TE = 3.57 ms values were slightly different in order to improve image quality, but all other parameters were exactly the same. To ensure the reliability and compatibility of the data, we compared the subjects scanned on the two scanners on socio-demographic and imaging parameters. There were no differences on age ($P = 0.377$), or years of education ($P = 0.588$), but more women were inadvertently scanned on Scanner B than A ($P = 0.003$). The volumetric measures of total intracranial volume (TIV), gray matter (GM) volume, white matter (WM) volume or cerebrospinal fluid (CSF) volume obtained from two scanners did not differ significantly.

Image analysis

The volumes of GM, WM and CSF were calculated after the segmentation of T1-weighted MRI using SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). ICV was measured as the sum of the total GM, WM and CSF, and total brain volume as the sum of total grey and white matter. The volumes of brain anatomical regions were determined by manually outlining the periphery of the ROI on the coronal T1-weighted slices using Analyze 5.0 (Brain Imaging Resource, Mayo Clinic, Rochester, MI, USA). The outlining of the structures always proceeded from anterior to posterior, and the amygdala was traced first. Amygdalar tracing began a maximum number of four slices anterior to the slice where the anterior tip of the temporal horn was visible, and was traced according to the protocol outlined by Watson *et al.* (1997). In addition, the hippocampal tail was manually traced according to the protocol described in detail in Maller *et al.* (2006). Volume estimations were repeated on 10 randomly selected scans and inter-class correlations were 0.997 for the right and 0.995 for the left, indicating high inter-rater reliability.

Measurement of behavioural inhibition and behavioural activation (BIS/BAS)

BIS/BAS measures consisted of a single scale representing BIS (7 items; Cronbach's alpha = 0.80), and three separate indices representing elements of the BAS: BAS-D (4 items; Cronbach's alpha = 0.84), BAS-FS (4 items; Cronbach's alpha = 0.71) and BAS-RR (5 items; Cronbach's alpha = 0.72) (Carver and White, 1994). Higher scores on the indices represent a greater identification with the construct. The factor structure of the BIS–BAS initially proposed by Carver and White (1994) has been validated in culturally diverse samples (Leone *et al.*, 2001) and reliability coefficients ranging from 0.65 to 0.83 for the four scales have been reported in a community sample (Jorm *et al.*, 2007).

Statistical analysis

Multiple regression analyses were conducted to determine whether hippocampal volume, amygdalar volume and hippocampal and amygdalar lateralization indexes [calculated with the formula (L−R)/(L + R)] predicted BIS and BAS measures while controlling for sex, age, education, ICV and total brain volume. The confounding variables were entered in a first model, followed by the factors of interest in a second model, and finally the interactions between sex and the hippocampal and amygdalar measures. Since in all analyses, none of the interactions contributed significantly to the previous models, models including interactions were not reported. The models were reduced by progressively removing variables that did not reach significance (variables were kept in the model if they approached significance and $P < 0.08$). P was set at 0.01 to reduce the probability of Type I errors resulting from multiple significance testing. The same analyses were conducted for the whole sample and for a sub-sample that excluded participants who reported using anti-depressive drugs since the relationships between hippocampal and amygdalar volumes and BIS/BAS measures may differ.

RESULTS

Summary statistics pertaining to demographic characteristics and brain measures of subjects in the study are shown in Table 1. Females had lower ICV, hippocampal and amygdalar volumes than males but did not differ in their laterality

indexes, age or education level. Females reported greater BIS sensitivity, while males reported higher levels of BAS-D. The strength of association between the BIS and the different BAS scales are presented in Table 2 and show that the BIS was only significantly correlated with the BAS-RR measures while all BAS scales were significantly inter-correlated.

No significant association was found between brain predictors and BAS-F and BAS-D after adjusting for confounding variables. Tables 3 and 4 show results of multiple regression analyses predicting BIS and BAS-RR for the whole sample and participants who did not report anti-depressive medication. Total hippocampal and amygdalar volumes, hippocampal and amygdalar laterality indexes, as well as interactions between sex and brain measures, were included as independent variables while controlling for age, sex, education level and intra-cranial and total brain volume. None of the interactions with sex were significant and are therefore not reported. Significant R^2 change associated with each BIS/BAS predictor is reported at the end of each table. The BIS was significantly positively associated with total hippocampal volume but more so for participants who did not report anti-depressive medication. For the reward responsiveness measure of the BAS, a trend was present suggesting an association between greater hippocampal volume and greater sensitivity to reward. None of the laterality indexes were found to be significant predictors. Figure 1 shows scatter plots of the BIS and BAS measures and hippocampal volume.

Since the BIS and the BAS-RR scale were significantly correlated and significant (trend for BAS-RR) predictors of hippocampal volume another regression analysis was conducted to determine whether the BAS-RR measure explained variance in hippocampal volume beyond that already explained by the BIS. The BIS alone was found to be a significant predictor of hippocampal volume (Table 5).

Table 1 Demographic characteristics and brain measures of the study sample

	Males ($n = 197$)	Females ($n = 233$)	*df*	*t*	*P*
Age (years)	46.63 (1.51)	46.73 (1.37)	428	−0.691	0.490
Education (years)	15.01 (2.22)	14.60 (2.30)	428	1.867	0.063
Depression medication (%)	11 (5.6)	20 (8.6)	428	1.436	0.231
BIS	19.86 (3.46)	21.41 (3.36)	428	−4.723	0.000**
BAS-FS	11.03 (2.16)	10.95 (2.09)	428	0.371	0.711
BAS-RR	16.27 (2.04)	16.70 (2.10)	428	−2.148	0.033
BAS-D	10.31 (2.49)	9.52 (2.47)	428	3.331	0.001**
Hippocampal volume (ml)	5.54 (0.76)	5.06 (0.57)	428	7.439	0.000**
Hippocampal laterality index	−0.03 (0.14)	0.03 (0.10)	428	−0.483	0.629
Amygdalar volume (ml)	2.79 (0.39)	2.48 (0.36)	428	8.599	0.000**
Amygdalar laterality index	0.00 (0.06)	−0.01 (0.07)	428	0.849	0.397
ICV (litres)	1.55 (0.11)	1.37 (0.10)	428	18.131	0.000**

**Significant at 0.001 level; brain measures are uncorrected raw volumes.

DISCUSSION

The findings of the present study support the view that the septo-hippocampal system in humans is related to the BIS measure developed by Carver and White (1994), which is thought to be a reliable index of the BIS described by Gray and McNaughton 2003; McNaughton and Gray, 2000.

As expected, behavioural inhibition was associated with hippocampal volume, with larger volumes being associated with greater levels of inhibition. Approximately 3% of the variance in BIS above and beyond that predicted by covariates (sex, age, education, intra-cranial volume and total

Table 2 Correlations between BIS and BAS measures

	BAS-D	BAS-FS	BAS-RR
BIS	−0.080	−0.028	0.369**
BAS-D		0.595**	0.462**
BAS-FS			0.512**

**Significant at the 0.01 level (2-tailed).

Table 3 Predictors of BIS assessed by multiple regression with hippocampal and amygdalar volume and laterality indexes as predictors, and controlled for education, age, sex, intra-cranial volume and total brain volume for the whole sample and for participants without depression medication

	All participants ($N = 430$)				Participants without treatment for depression ($N = 399$)			
	Full		Reduced		Full		Reduced	
	β	*P*	β	*P*	β	*P*	β	*P*
Predictors								
Hip Vol.	**0.190**	**0.025**	**0.167**	**0.002**	**0.228**	**0.009**	**0.203**	**0.000**
Hip Lat.	−0.022	0.730			−0.023	0.724		
Amyg Vol.	−0.053	0.494			−0.058	0.474		
Amyg Lat	0.057	0.434			0.045	0.540		
	R^2 (Change)	*P*	R^2 (Change)	*P*	R^2 (Change)	*P*	R^2 (Change)	*P*
Predictors	0.086 (0.026*)	0.019	0.082 (0.022**)	<0.001	0.103 (0.035**)	<0.001	0.097 (0.029*)	<0.001

*0.05 and **0.01 significant R^2 change from previous model; All models controlled for sex, age, education, intra-cranial volume, total brain and volume.

Table 4 Predictors of behavioural activation reward scale assessed by multiple regression with hippocampal and amygdalar volume and laterality indexes as predictors, and controlled for education, age, sex, intra-cranial volume and total brain volume for the whole sample and for participants without depression medication

	All participants ($N = 430$)				Participants without treatment for depression ($N = 399$)			
	Full		Reduced		Full		Reduced	
	β	P	β	P	β	P	β	P
Predictors								
Hip Vol.	0.128	0.044	0.106	0.066	0.139	0.035	0.127	0.035
Hip Lat.	0.029	0.558			0.060	0.238		
Amyg Vol.	−0.058	0.352			−0.040	0.541		
Amyg Lat	−0.028	0.561			−0.049	0.332		
	R^2 (Change)	P	R^2 (Change)	P	R^2 (Change)	P	R^2 (Change)	P
Predictors	0.027 (0.012)	0.231	0.023 (0.008)	<0.121	0.030 (0.018)	<0.122	0.023 (0.011*)	<0.035

*0.05 and **0.01 significant R^2 change from previous model; All models controlled for sex, age, education, intra-cranial volume, total brain volume.

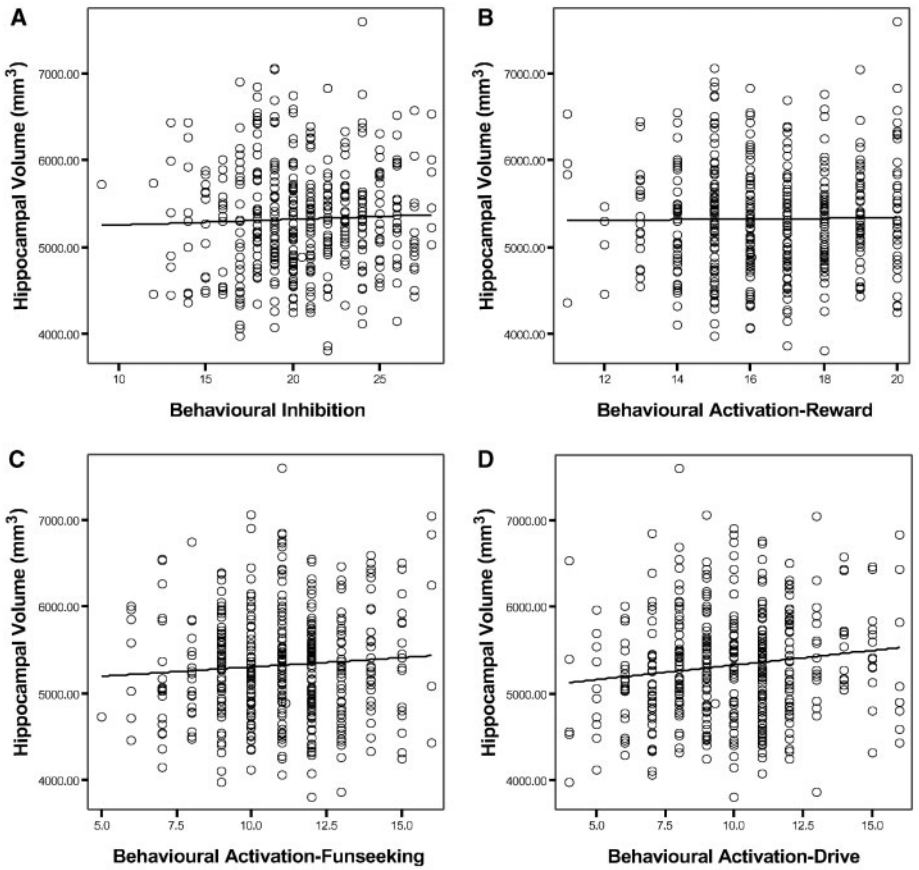

Fig. 1 Scatter plots of the unadjusted association between hippocampal volume and BIS (**A**), BAS-RR (**B**), BAS-FS (**C**) and BAS-D (**D**).

brain volume) was predicted by hippocampal volume. This is consistent with previous finding showing a positive association between hippocampal volume and the BIS (Barros-Loscertales *et al.*, 2006a), and a positive relationship between hippocampal volume and anxiety (Rusch *et al.*, 2001). In contrast, amygdalar volume which was expected to be positively related to behavioural inhibition was not a significant BIS predictor. This finding might reflect the fact that previous studies have related the BIS to physiological activation of the amygdala in imaging studies and not to volumetric measures (Cools *et al.*, 2005). Thus, for the amygdala, greater volume might not equate to greater activation. However, Barros-Loscertales *et al.* (2006a) did demonstrate a positive association between BIS and amygdalar volume. Alternatively, since the present study did not select participants based on the presence of clinical symptoms, the

Table 5 Predictors of hippocampal volume assessed by multiple regression with BIS and BAS-RR as predictors, and controlled for education, age, sex, intra-cranial volume and total brain volume for the whole sample and for participants without depression medication

	All participants ($N = 430$)				Participants without treatment for depression ($N = 399$)			
	Full		Reduced		Full		Reduced	
	β	P	β	P	β	P	β	P
Predictors								
BIS	**0.118**	**0.008**	**0.130**	**0.002**	**0.136**	**0.003**	**0.151**	**<0.001**
BAS-RR	0.035	0.413			0.041	0.361		
	R^2 (Change)	P	R^2 (Change)	P	R^2 (Change)	P	R^2 (Change)	P
Predictors	0.324 (0.017**)	<0.001	0.323 (0.016**)	<0.001	0.328 (0.023**)	<0.001	0.037 (0.021)	<0.001

*0.05 and **0.01 significant R^2 change from previous model; All models controlled for sex, age, education, intra-cranial volume, total brain volume.

range of the independent and dependent variables might have been too restricted. This latter suggestion, however, is contradicted by the findings that a weaker association was present between amygdalar volume and BIS in the whole sample, and stronger when those taking depression medication were excluded. Another possibility is that this association is present in younger adults as studied by Barros-Loscertales *et al.* but not in middle-aged adults, as sampled in this study.

A weak association was also found between the reward responsiveness measure of the BAS and larger hippocampal volumes. The fact that this association follows the same direction as that found between the BIS and hippocampal volume suggests that the hippocampus might be involved in modulating the intensity rather than the direction of the BIS and BAS, possibly by filtering distal signals communicated via the hypothalamus, striatum and through cortical connections. Since Gray and McNaughton's revised model (2003, 2006) suggests that the hippocampus acts as a comparator assessing conflict between simultaneous goals, an association with both the BIS and the BAS might not be so surprising and might serve to optimize potentially conflicting outcomes, both in terms of withdrawal and approach behaviours, by minimizing punishment (BIS) and maximizing reward (BAS). Alternatively, these findings might be due to problems in the construct validity of the BAS-RR scale. Previous research (Heubeck *et al.*, 1998) has questioned the validity of this sub-scale due to its unexpected association with the BIS and its low association with a measure of reward dependence which it is meant to reflect. Since the BAS-RR measure did not predict hippocampal volume above and beyond that predicted by the BIS measure in the *post hoc* analysis, and given a moderate but significant correlation between BIS and BAS-RR measures, it is possible that the BAS measure is partly contaminated by a BIS component and that greater behavioural activation is not associated with a larger hippocampus.

No laterality effect was present. This is somewhat surprising since emotion research suggests that the right hemisphere and particularly the right amygdala are involved in the modulation of negative affect and anxiety (Davidson, 2001). However, it is possible that this asymmetrical effect is predominantly mediated not by size but by level of activation which in turn might be modulated by asymmetrical activation of the prefrontal cortex.

This study had a number of strengths but also a number of limitations. The sample used was recruited from a large randomly selected community-based sample and therefore is likely to be more representative of the general population than clinical sample and smaller studies. Furthermore, hippocampal and amygdalar volumes were manually traced by an expert neuroscientist and analyses controlled for intracranial and total brain volume and therefore, unlike studies based on grey matter density (voxel-based morphometry), results reflect the association between BIS/BAS and the specific structures studied with a high level of confidence. However, only a sub-sample of the relevant cerebral structures were investigated and therefore the present findings only present a partial picture of the neuroanatomical structures associated with the BIS/BAS. It could also be argued that the association presented in this article might be largely due to an unidentified sub-sample of participants with mood-disorders. To address this question we have conducted two sets of analyses, one on the whole sample and a second on a sub-sample of participants who did not report anti-depressant medication. The stronger associations evident in the latter analysis suggest that hippocampal volumes are related to BIS characteristics in psychologically healthy individuals. However, assessing the effect of anti-depressant medication is not equivalent to controlling for mood disorders and psychiatric morbidity. It may be that the association between BIS and hippocampal volume differ between individuals who suffer from mood disorders but do not take anti-depressant medication, and individuals who do not suffer from mood disorders. Finally, since the BIS measure developed by Carver and White has been shown to be associated with personality factors such as neuroticism, it is possible that the present results reflect an association between the BIS and constructs other than the behavioural inhibition system. These issues will need to be addressed in future research.

In conclusion, a clear positive volumetric association between hippocampal volume and the BIS scale developed by Carver and White (1994), which is thought to be a good index of Gray's behavioural inhibition system, was demonstrated in a large cognitively intact community-based sample, but contrary to predictions, no significant association was found between amygdalar volume and the BIS or the BAS.

REFERENCES

Barros-Loscertales, A., Meseguer, V., Sanjuan, A., et al. (2006a). Behavioral inhibition system activity is associated with increased amygdala and hippocampal gray matter volume: a voxel-based morphometry study. *Neuroimage*, *33*(3), 1011–5.

Barros-Loscertales, A., Meseguer, V., Sanjuan, A., et al. (2006b). Striatum gray matter reduction in males with an overactive behavioral activation system. *European Journal of Neuroscience*, *24*(7), 2071–4.

Beaver, J.D., Lawrence, A.D., van Ditzhuijzen, J., Davis, M.H., Woods, A., Calder, A.J. (2006). Individual differences in reward drive predict neural responses to images of food. *Journal of Neuroscience*, *26*(19), 5160–5166.

Campbell-Sills, L., Liverant, G.I., Brown, T.A. (2004). Psychometric evaluation of the behavioral inhibition/behavioral activation scales in a large sample of outpatients with anxiety and mood disorders. *Psychological Assessment*, *16*(3), 244–54.

Carver, C.S., White, T.L. (1994). Behavioral inihibition, behavioral activation, and affective reponses to impending reward and punishment: the BIS/BAS scales. *Journal of Personality and Social Psychology*, *67*, 319–33.

Colla, M., Kronenberg, G., Deuschle, M., et al. (2007). Hippocampal volume reduction and HPA-system activity in major depression. *Journal of Psychiatric Research*, *41*(7), 553–60.

Cools, R., Calder, A.J., Lawrence, A.D., Clark, L., Bullmore, E., Robbins, T.W. (2005). Individual differences in threat sensitivity predict serotonergic modulation of amygdala response to fearful faces. *Psychopharmacology (Berl)*, *180*(4), 670–9.

Davidson, R.J. (2001). Toward a biology of personality and emotion. *Annals of the New York Academy of Sciences*, *935*, 191–207.

Dawe, S., Loxton, N.J. (2004). The role of impulsivity in the development of substance use and eating disorders. *Neuroscience and Biobehavioral Reviews*, *28*(3), 343–51.

Gray, J.A. (1970). The psychophysiological basis of introversion-extraversion. *Behaviour Research and Therapy*, *8*(3), 249–66.

Gray, J.A. (1981). *A Critique of Eysenk's Theory of Personality*. Berlin: Springer.

Gray, J.A., and McNaughton, N. (2003). *The Neuropsychology of Anxiety: an Enquiry in to the Function of the Septo-hippocampal System*, 2nd edn. Oxford: Oxford University Press.

Gray, J.R., Burgess, G.C., Schaefer, A., Yarkoni, T., Larsen, R.J., Braver, T.S. (2005). Affective personality differences in neural processing efficiency confirmed using fMRI. *Cognitive, Affective & Behavioral Neuroscience*, *5*(2), 182–90.

Heubeck, B., Wilkinson, R., Cologon, J. (1998). A second look at Carver and White's (1994) BIS/BAS scales. *Personality and Individual Differences*, *25*, 785–800.

Hewig, J., Hagemann, D., Seifert, J., Naumann, E., Bartussek, D. (2006). The relation of cortical activity and BIS/BAS on the trait level. *Biological Psychology*, *71*(1), 42–53.

Jorm, A.F., Mather, K.A., Butterworth, P., Anstey, K.J., Christensen, H., Easteal, S. (2007). APOE genotype and cognitive functioning in a large age-stratified population sample. *Neuropsychology*, *21*(1), 1–8.

Kalisch, R., Schubert, M., Jacob, W., et al. (2005). Anxiety and hippocampus volume in the rat. *Neuropsychopharmacology*, *31*(5), 925–32.

Konarski, J.Z., McIntyre, R.S., Kennedy, S.H., Rafi-Tari, S., Soczynska, J.K., Ketter, T.A. (2008). Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. *Bipolar Disorders*, *10*(1), 1–37.

Leone, L., Perugini, M., Bagozzi, R.P., Pierro, A., Mannetti, L. (2001). Construct validity and generalizability of the Carver-White Behavioural Inhibition/Behavioural Activation scales. *European Journal of Personality*, *15*, 373–90.

Maller, J.J., Reglade-Meslin, C., Anstey, K.J., Sachdev, P. (2006). Sex and symmetry differences in hippocampal volumetrics: before and beyond the opening of the crus of the fornix. *Hippocampus*, *16*(1), 80–90.

McNaughton, N. (2006). The role of the subiculum within the behavioural inhibition system. *Behavioural Brain Research*, *174*(2), 232–50.

McNaughton, N., Gray, J.A. (2000). Anxiolytic action on the behavioural inhibition system implies multiple types of arousal contribute to anxiety. *Journal of Affective Disorders*, *61*(3), 161–76.

Muris, P., Meesters, C., van den Hout, A., Wessels, S., Franken, I., Rassin, E. (2007). Personality and temperament correlates of pain catastrophizing in young adolescents. *Child Psychiatry and Human Development*, *38*(3), 171–81.

O'Brien, J.T., Lloyd, A., McKeith, I., Gholkar, A., Ferrier, N. (2004). A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *The American Journal of Psychiatry*, *161*(11), 2081–90.

Ozer, D.J., Benet-Martinez, V. (2006). Personality and the prediction of consequential outcomes. *Annual Review of Psychology*, *57*, 401–21.

Perkins, A.M., Corr, P.J. (2006). Reactions to threat and personality: psychometric differentiation of intensity and direction dimensions of human defensive behaviour. *Behavioural Brain Research*, *169*(1), 21–8.

Reuter, M., Schmitz, A., Corr, P., Hennig, J. (2006). Molecular genetics support Gray's personality theory: the interaction of COMT and DRD2 polymorphisms predicts the behavioural approach system. *The International Journal of Neuropsychopharmacology*, *9*(2), 155–66.

Rusch, B.D., Abercrombie, H.C., Oakes, T.R., Schaefer, S.M., Davidson, R.J. (2001). Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. *Biological Psychiatry*, *50*(12), 960–4.

Sigurdsson, T., Doyere, V., Cain, C.K., LeDoux, J.E. (2007). Long-term potentiation in the amygdala: a cellular mechanism of fear learning and memory. *Neuropharmacology*, *52*(1), 215–27.

Smillie, L.D., Pickering, A.D., Jackson, C.J. (2006). The new reinforcement sensitivity theory: implications for personality measurement. *Personality and Social Psychology Review*, *10*(4), 320–35.

Watson, C., Jack, C.R., Cendes, F. (1997). Volumetric magnetic resonance imaging. Clinical applications and contributions to the understanding of temproal lobe epilepsy. *Archives of Neurology*, *9*, 97–113.

Wright, C.I., Williams, D., Feczko, E., et al. (2006). Neuroanatomical correlates of extraversion and neuroticism. *Cerebral Cortex*, *16*(12), 1809–19.

Yamasue, H., Abe, O., Suga, M., et al. (2008). Gender-common and -specific neuroanatomical basis of human anxiety-related personality traits. *Cerebral Cortex*, *18*(1), 46–52.

Zetzsche, T., Preuss, U.W., Frodl, T., et al. (2007). Hippocampal volume reduction and history of aggressive behaviour in patients with borderline personality disorder. *Psychiatry Research*, *154*(2), 157–70.