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RAPID COMMUNICATION

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Selective impairment in the recognition of anger induced by diazepam

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Abstract *Rationale:* Facial expressions appear to be processed by at least partially separable neuro-cognitive systems. Given this functional specialisation of expression processing, it is plausible that these neurocognitive systems may also be dissociable pharmacologically. *Objective:* The present study therefore compared the effects of diazepam (15 mg) with placebo upon the ability to recognise emotional expressions. *Methods:* A double blind, independent group design was used to compare the effects of diazepam and matched placebo in 32 healthy volunteers. Participants were presented morphed facial expression stimuli following a paradigm developed for use with patients with brain damage and asked to name one of the six basic emotions (sadness, happiness, anger, disgust, fear and surprise). *Results:* Diazepam selectively impaired subjects' ability to recognise angry expressions but did not affect recognition of any other emotional expression. *Conclusions:* The findings are interpreted as providing further support for the suggestion that there are dissociable systems responsible for processing emotional expressions. It is suggested that these findings may have implications for understanding paradoxical aggression sometimes elicited by benzodiazepines.

Key words Diazepam · Emotion · Emotional expression

Introduction

Facial expressions appear to be processed by at least partially separable neuro-cognitive systems (e.g. Adolphs et al. 1996; Blair et al. 1999). Thus, for example, neuropsychological and neuro-imaging studies have demonstrated the role of the amygdala in processing fearful expressions. Patients with lesions to the temporal lobe, including the amygdala, often fail to recognise fearful expressions (e.g. Adolphs et al. 1994; Calder et al. 1996; though not always: Hamann et al. 1996). Functional imaging studies consistently report increased activation in the left amygdala to presentation of fearful expressions (e.g. Morris et al. 1996; Phillips et al. 1997). A recent neuro-imaging study has indicated that the amygdala is also involved in processing sad expressions (Blair et al. 1999). As regards disgust expressions, both basal ganglia and insula have been implicated (e.g. Sprengelmeyer et al. 1996; Gray et al. 1997; Phillips et al. 1997). Patients with Huntingdon's disease, which initially affects the basal ganglia and caudate nucleus, show impaired recognition of the expression of disgust (Gray et al. 1997; Sprengelmeyer et al. 1996). However, a functional magnetic resonance imaging (fMRI) study of subjects exposed to expressions of disgust failed to identify basal ganglia activation though it did reveal activation of anterior insula (Phillips et al. 1997). Anterior insula has been implicated in responding to offensive tastes (e.g. Kinomura et al. 1994; Zald et al. 1998). Right orbitofrontal cortex appears implicated in the response to angry expressions (Blair et al. 1999).

Thus, both neuropsychological and neuro-imaging studies indicate the existence of separable neuro-cognitive circuits processing expression stimuli. Given this functional specialisation of expression processing, it is plausible that these separable neurocognitive circuits may also be dissociable pharmacologically. The impact of the benzodiazepines on many cognitive systems, for example memory, have been studied extensively (e.g. see Ghoneim and Mewaldt 1990; Curran 1991; Curran et al. 1998 for reviews). Pharmacological dissociations of memory systems have often complimented dissociations made functionally, developmentally or in studies of organic amnesia (Nyberg and Tulving 1997; Curran 1999).

As far as we are aware, the current study is the first to investigate the implications of the benzodiazepines on the processing of emotional expressions. Areas contain-

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ing high levels of benzodiazepine receptor sites in the brain include the amygdala and frontal cortex (e.g. Dennis et al. 1988). Typically, the anxiolytic effects of the benzodiazepines have been thought to occur in the amygdala (e.g. Stroessner et al. 1989; Patrick et al. 1996). On the basis of the neuropsychological literature (e.g. Calder et al. 1996), if diazepam affects the amygdala selectively we can predict impairment in the recognition of fearful expressions. Contrasting predictions are possible. Frontal cortex, particularly right orbitofrontal cortex, has been implicated in the processing of angry expressions (Blair et al. 1999). If diazepam affects orbitofrontal cortex, we can predict impairment in the recognition of angry expressions. Finally, if diazepam has generalised effects, we can predict general impairment in the recognition of expressions. The current study explores these contrasting predictions.

Materials and methods

Thirty-two volunteers (14 men and 18 women) aged 20–43 years (mean age 27.4 years) participated in the study. All were healthy, taking no medication and with no history of important medical or psychiatric disease. The study had ethical committee approval and all subjects gave written informed consent. Subjects were randomly allocated to one of two parallel groups according to pharmacological treatment (diazepam versus placebo). Diazepam (15 mg) and placebo were formulated in identical opaque gelatin capsules and given orally. The testing session began 40 min after ingestion of the capsule. The subjects were given the Mood Rating Scale (Bond and Lader 1974) to complete both before treatment and after completing the recognition task to provide a measure of diazepam's sedative and anxiolytic effects.

The task was based on the paradigm described by Calder et al. (1996). This method assesses recognition of six emotion expressions: surprise, happiness, anger, disgust, sadness and fearfulness. The stimuli are continuous tone images where two expressions have been morphed together. The expressions are morphed from one to the next over a series of five stages. This was achieved by taking the two prototypes of each emotion and stretching them across so that "all the points representing the same features were aligned across images" (Calder et al. 1996). The emotion blends are, for example, 90% anger-10% happiness, 70% anger-30% happiness, 50% anger-50% happiness, 30% anger-70% happiness, 10% anger-90% happiness. The expressions morphed are anger to happiness, happiness to surprise, surprise to fearfulness, fearfulness to sadness, sadness to disgust and disgust back to anger. All the stimuli involve the face JJ (Ekman and Friesen 1976). There were 30 faces in total.

Each face was presented to the participant on a computer screen with each stimulus subtending a horizontal visual angle of 3.6 degrees and a vertical angle of 5.2 degrees. There were six blocks of stimuli. In each block, all 30 stimuli were presented in a randomised order. The first block was counted as practice trials and the data for these trials is not recorded. Each stimulus was presented for 3 s and there was a 4- to 6-s interval between each stimulus, during which the screen was blank. Each subject was presented with a list of six response options (surprise, happiness, anger, disgust, sadness and fearfulness) and instructed to name the expression being displayed.

Results

Table 1 summarises the participant characteristics, data on arousal/ sedation and expression recognition data as a function of pharmacological intervention. As participant groups did not differ significantly in either gender, age or weight, one-way analyses of variance (ANOVAs) were used to compare diazepam and placebo effects on the participants' mood ratings (analysed as three mood factors; Bond and Lader 1974) and their ability to recognise the six basic emotions. These revealed first that there were significant sedative effects of diazepam [alertness factor: $F(1,30)=6.00$, $P<0.05$] and that there was a suggestion for such an effect for calmness [$F(1,30)=1.97$, $P<0.1$, one-tailed]. In addition, the ANOVAs revealed that diazepam had a highly selective effect on the recognition of angry expressions [$F(1,30)=5.22$; $P<0.03$]. Participants who had been administered diazepam were significantly less likely to recognise these expressions than those participants who had been administered placebo. In contrast, diazepam did not effect the recognition of any of the other expressions (see Table 1).

Table 1 Number of correct answers on the emotion attribution task (standard deviations and ranges in brackets)

	Placebo	Diazepam	$F(1,30)$	P
Gender	5 male 11 female	9 male 7 female	–	χ^2=NS
Age	28.88 (8.82)	25.81 (3.85)	1.97	NS
Weight	67.94 (13.28)	70.69 (11.70)	<1	NS
Alert	50.34 (13.48)	62.12 (13.73)	6.00	<0.05
Content	60.31 (8.28)	64.94 (10.22)	<1	NS
Calm	49.53 (11.49)	46.09 (12.05)	1.97	<0.1 (one-tailed)
Surprise	11.31 (0.95)	11.25 (0.93)	<1	NS
Happiness	11.94 (0.25)	11.94 (0.25)	<1	NS
Anger	11.56 (0.81)	9.75 (3.06)	5.22	<0.05
Disgust	10.81 (3.71)	9.63 (2.58)	1.11	NS
Sadness	11.06 (0.85)	11.00 (1.86)	<1	NS
Fearfulness	10.13 (2.12)	10.25 (1.88)	<1	NS

Discussion

The current study is, to our knowledge, the first investigation assessing whether expression recognition can be affected by a pharmacological manipulation. This study revealed that diazepam has a selective effect on the recognition of angry expressions. However, it did not affect the recognition of any of the other five expressions investigated. Thus, not only can the neuro-cognitive circuits mediating the responses to the basic emotion ex-

pressions be selectively affected by structural lesions, they can also be selectively affected by pharmacological manipulation.

Before we consider the theoretical implications of the present study, it is necessary to consider whether the results could be explained in terms of an experimental artefact. Could the specificity of the present results be attributable to a task difficulty effect? This would seem to be unlikely. Fearfulness is generally considered to be the most difficult expression to recognise (Ekman and Friesen 1974). Indeed, it is recognition of this expression which has most often been reported to be affected by anatomical lesions (e.g. Adolphs et al. 1996; Calder et al. 1996). However, diazepam did not influence the recognition of fearful expressions, only angry expressions. It thus appears that the present results cannot be attributed to task difficulty effects.

There is relatively widespread distribution of benzodiazepine receptor sites in the brain, with highest concentrations in the limbic system and throughout the cortex. Thus, both the amygdala and frontal cortex have significant concentrations (e.g. Dennis et al. 1988). Indeed, typically the anxiolytic effects of the benzodiazepines have been thought to occur via the amygdala (e.g. Stroessner et al. 1989; Patrick et al. 1996). However, an effect on amygdala activity would have predicted reduced recognition of fearful expressions. This did not occur. Instead, there was a selective effect on the recognition of angry expressions. While there have been suggestions that some patients with amygdala damage show impairment in the recognition of angry expressions, all of these patients have had far greater difficulty with the recognition of fear (e.g. Calder et al. 1996; Scott et al. 1997). Moreover, the majority of patients with amygdala lesions show no impairment in the recognition of anger (e.g. Adolphs et al. 1994; Calder et al. 1996; Broks et al. 1998). It would thus appear that the 15 mg dose of diazepam used in the present study was not sufficient to modulate the neuro-cognitive circuit including the amygdala that processes expressions (particularly those of fear). It is interesting to consider whether a higher dose of diazepam might be necessary to influence the recognition of fearful expressions. However, there is a more speculative alternative. There are many reports of diazepam modulating amygdala activity; e.g. a 15 mg dose is sufficient to reduce the augmentation of startle reflex response following a visual threat prime. Thus, the current data might suggest a degree of functional specialisation within the amygdala; i.e. diazepam may affect the circuit involved in the augmentation of startle reflex but not the circuit processing fearful expressions.

So what structures might be implicated in mediating the present results? While there is reasonable agreement concerning the anatomical structures involved in processing the expression of fear, much less is known about the anatomical structures implicated in processing the expression of anger. However, one strong candidate structure is orbitofrontal cortex. Orbitofrontal cortex has been implicated in both animal and human lesion studies in behavioural extinction and reversal learning (e.g. Dias et al. 1996; Rolls 1997). Angry expressions curtail the behaviour of others in situations where social rules or expectations have been violated and, in this sense, they are effectively used to terminate the on-going behaviour of others (e.g. Averill 1982). At least some individuals with orbitofrontal cortex lesions who no longer curtail their behaviour according to social rules and expectations, show striking impairment in the recognition of angry expressions (Blair and Cipolotti, submitted). In addition, a recent functional imaging study demonstrated a right orbitofrontal cortex response to angry expressions (Blair et al. 1999).

Considering the above evidence, we thus suggest that the 15 mg dose of diazepam was sufficient to disrupt the neuro-cognitive circuit that responds to angry expressions and which involves right orbitofrontal cortex. It may be that benzodiazepines have a more powerful effect on neurones in this area than in areas implicated in processing other emotional expressions. Diazepam has often been used to ameliorate not only “pure” anxiety states but also mixed anxiety-depression (Lader and Petursson 1983). Functional imaging studies have observed that depression is associated with bilateral hyperactivation of orbitofrontal cortex (e.g. Mayberg 1994, 1997). This is particularly interesting as a recent study investigating the expression recognition ability of depressed patients has shown that these patients show a selective hypersensitivity to angry expressions (Murray, Reid, Wheeldon et al., unpublished data). Moreover, the finding that at least some individuals who, following damage to orbitofrontal cortex, show high levels of socially aberrant behaviour including aggression is also of relevance here (Blair and Cipolotti, unpublished data). This is of interest because various clinical reports have detailed incidences of aggression following treatment with benzodiazepines varying from 10% in a mixed diagnostic group (Rosenbaum et al. 1984) to 58% in patients with borderline personality disorder (Gardner and Cowdry 1985). Controlled, laboratory studies have also shown that administration of benzodiazepines is associated with increased behavioural aggression following provocation in both anxious patients undergoing benzodiazepine treatment (Bond et al. 1995) and healthy volunteers administered only one dose of a benzodiazepine (Bond and Silveira 1993).

In summary, the present study found that diazepam selectively impairs the ability to recognise angry expressions. This finding further supports the notion that there are separable neuro-cognitive mechanisms involved in the processing of the different emotional expressions (e.g. Adolphs et al. 1996; Blair et al. 1999).

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