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The functional neuroimaging of human emotion: Asymmetric contributions of cortical and subcortical circuitry

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I. INTRODUCTION

Affective neuroscience is the subdiscipline of the biobehavioral sciences that examines the underlying neural bases of mood and emotion. The application of this body of theory and data to the study of normal emotion, disorders of emotion and affective style is helping to generate a new understanding of the brain circuitry underlying these phenomena. Moreover, parsing the heterogeneity of both normal and abnormal emotional processes on the basis of known circuits in the brain is providing a novel and potentially very fruitful approach to classification and subtyping that does not rely on the descriptive nosology of personality theory and psychiatric diagnosis but rather is based upon more objective characterization of specific affective processing deficits in normal individuals and in patients with mood disorders. At a more general level, this approach is helping to bridge the wide chasm between the literatures that have focused on normal emotion and the disorders of emotion. Historically, these research traditions have had little to do with one another and have emerged completely independently. However, affective neuroscience has helped to integrate these approaches into a more unified project that is focused upon the understanding of normal and pathological individual differences in affective style, its constituent components and their neural bases (see e.g., Davidson et al., 2000a, Davidson, 2000).

Affective neuroscience takes as its overall aims a project that is similar to that pursued by its cognate discipline, cognitive neuroscience, though focused instead on affective processes. The decomposition of cognitive processes into more elementary constituents that can then be studied in neural terms has been remarkably successful. We no longer query subjects about the contents of their cognitive processes since many of the processes so central to important aspects of cognitive function are opaque to consciousness. Instead, modern cognitive scientists and

neuroscientists have developed laboratory tasks to interrogate and reveal more elementary cognitive function. These more elementary processes can then be studied using imaging methods in humans, lesion methods in animals and the study of human patients with focal brain damage. Affective neuroscience approaches emotion using the same strategy. Global constructs of emotion are giving way to more specific and elementary constituents that can be examined with objective laboratory measures. For example, the time course of emotional responding and the mechanisms that are brought into play during the regulation of emotion can now be probed using objective laboratory measures. These constructs may be particularly important for understanding mood disorders since patients with depression may suffer from abnormalities in emotion regulation and persistence of negative affect. Patients with such abnormalities may differ from those whose primary deficit may be in reactivity to positive incentives.

Previously constructs such as emotion regulation have mostly been gleaned from self-report measures whose validity has been seriously questioned (e.g., Kahneman, 1999). While the phenomenology of emotion provides critical information to the subject that helps guide behavior it may not be a particularly good source for making inferences about the processes and mechanisms that underlie emotion and its regulation. Though it is still tempting and often important to obtain measures of subject's conscious experience of the contents of their emotional states and traits, these no longer constitute the sole source of information about emotion.

This review will feature data that have mostly been derived from human neuroimaging studies. Neuroimaging methods provide unique in vivo data on human brain function that can be then be associated with behavioral and/or self-report measures. Since certain mechanisms of emotion may differ in humans compared with other species (e.g., subjective experiences of emotion; more well-developed capacity for emotion regulation), the opportunity to study these questions in humans with methods that allow for the interrogation of brain function throughout

the brain volume is very significant. Some methods allow for the assessment of the time course of neural activation (e.g., event-related functional magnetic resonance imaging; fMRI) and other methods permit inferences to be drawn about connectivity among brain regions. Finally, positron emission tomography (PET) enables the investigator to probe the neurochemistry of the brain and evaluate how it may be affected by behavioral challenges.

The major limitation of the evidence derived from neuroimaging studies is that the data are correlative in nature and it is therefore difficult to make causal inferences about the role of specific circuits in behavior. However, when neuroimaging data in humans are combined with more invasive studies in animals where the same circuitry can be directly manipulated, powerful strategies become available for making causal inferences.

This review will focus on selected fMRI and PET studies published between 1993 and 2001 that specifically manipulated affect or investigated emotional processing and that bear on our understanding of asymmetries in the underlying neural circuitry. We will not treat studies that involve primarily the perception of emotional information such as facial expressions, for example. While interesting and important and clearly relevant to the perception of emotional information, these findings may not directly bear on our understanding of the neural substrates of emotion per se, despite the fact that such data are often casually interpreted as if the perception and production of emotion were necessarily utilizing the identical circuitry. We will also primarily focus upon studies in normal subjects since we have recently published several reviews of similar questions in psychiatric patients (Davidson et al., 2000b; Davidson et al., 2002). However, when pertinent, data from patient studies as well as from animal studies will be briefly mentioned.

II. CONCEPTUAL AND METHODOLOGICAL CONSIDERATIONS IN NEUROIMAGING STUDIES OF EMOTION AND AFFECTIVE STYLE

PET and fMRI provide powerful and complementary information that has not been possible to acquire with other methods. These techniques enable scientists to examine regional patterns of activation in normal intact humans with considerable spatial precision and, in the case of fMRI, with temporal resolution on the order of seconds. With PET, in addition to its use as a measure of hemodynamic or metabolic activity, it can also be used to probe components of neurotransmission in vivo in relation to behavioral performance (e.g., Koepp et al., 1998). The application of these methods to the study of emotion has burgeoned over the past several years and has generated a new corpus of literature on the circuitry associated with selective features of emotional responding and affective traits. There are a number of critical conceptual and methodological issues that are fundamental to neuroimaging studies of emotion that are highlighted below:

1. **The perception of emotional information must be carefully distinguished from the production of emotion.** There are many studies that present as stimuli to subjects, facial expressions of emotion. The presentation of facial expressions of emotion does not necessarily (nor even likely) elicit any emotion. Thus, when investigators use this procedure it is important that it be described as a study of the perception of emotional faces and not a study about emotion per se.
2. **The control conditions against which emotion activation is compared crucially influences the nature of the data obtained.** When using subtractive methodology, it is helpful to control for as much of the stimulus content as possible to isolate the effects of emotion per se. Thus, for example, the comparison of a condition during which subjects were

self-generating emotional imagery to a resting baseline would be problematic (e.g., Pardo et al., 1993) because any effects observed might not be a function of the particular emotion that was aroused, but rather the cognitive processes involved in retrieving information from memory and voluntarily generating visual imagery. It is good practice to include more than one emotion condition (e.g., both positive and negative) since any effect produced as a consequence of simply generating emotion per se should be common to the two emotions, while differences between conditions can be attributed to the specific nature of the emotional process elicited.

3. **Stimuli designed to elicit different emotions must be matched on arousal and physical characteristics.** Arousal can be inferred in several different ways including self-report and skin conductance measures. Differences in patterns of activation observed between two emotion conditions that are not matched on intensity or arousal can obviously result from a failure to match appropriately and might be more a function of the arousal differences rather than the emotion differences between conditions (see Davidson et al., 1990, for more extended discussion). A related issue is the need to match stimuli across emotion and control conditions on physical properties such as color, the presence of faces, spatial frequency etc. Some differences found between emotion conditions might conceivably be a function of physical differences between the stimuli that have nothing directly to do with emotion.
4. **Putatively asymmetric effects must be rigorously statistically interrogated.** Many investigators using both PET and fMRI have reported asymmetric changes associated with emotion. In most cases, claims about an activation being asymmetric were made on the basis of voxels in one hemisphere that exceeded statistical threshold while homologous voxels in the opposite hemisphere did not. However, such an analytic strategy, while typical, is only testing for main effects of condition. To demonstrate an actual difference between the two

hemispheres, it is necessary to test the Condition X Hemisphere or Group X Hemisphere interaction. The fact that such tests are rarely performed is largely a function of the fact that while conceptually straightforward, the implementation is complex for a variety of reasons including the lack of availability of commercial software for this purpose and most importantly, the fact that brains are not anatomically symmetric and thus it would be hazardous to simply identify the homologous region of the brain to evaluate a putatively asymmetric effect. Having said this, it must be quickly noted that such tests would still represent a considerable improvement over what is now standard practice. If the Hemisphere X Condition or Hemisphere X Condition interaction is not statistically significant, it is not legitimate to claim that an asymmetric finding is present since the lack of a significant interaction means that the changes found in one hemisphere are not significantly different from those observed in the other, even if the effects are independently significant in one hemisphere but not in the other. Moreover, it is possible for significant interactions to arise in the absence of any significant main effects.

These methodological obstacles for making inferences about patterns of asymmetric activation can be further worsened if the signal-to-noise ratio (SNR) within regions of interest is inhomogeneous as something can occur with fMRI. This latter problem could especially pertain to subcortical regions, such as the amygdala. Recently, LaBar and colleagues (2001) explicitly tested the hypothesis that "asymmetrical" results in task-related amygdalar activation may be artificially caused by SNR drop-outs due to susceptibility artifacts from the adjacent sinus. The authors used an algorithm to generate SNR maps thresholded at the minimum SNR required to observe reliable activation for a given fMRI protocol. The results showed that SNR was crucial for explaining variability in the pattern of amygdala activation across subjects: unilateral activation, bilateral activation, or no activation were highly

dependent on the SNR in the amygdalar region. These findings underscore the care and caution that is required in the interpretation of asymmetric findings with certain neuroimaging methods such as fMRI.

5. **The processes of emotion regulation must ultimately be disentangled from those associated with the generation of emotion per se.** Mechanisms that regulate emotion—those processes that maintain, enhance or suppress an emotion—are activated coterminously with the generation of emotion. This complicates the task of the scientist examining neuroimaging data and making inferences about the activations that are putatively associated with the elicited emotion. Some of the activations that have been observed could conceivably be a part of circuitry that serves to regulate emotion. While this topic is complex and has important conceptual and methodological implications, it cannot be treated extensively here other than to suggest at the outset that some of the inconsistencies that plague this literature may be associated with unintended variations in emotion regulation. Explicit manipulation of regulatory parameters may be one method for addressing this problem (see Davidson et al., 2000b for review).

III. REVIEW OF HUMAN NEUROIMAGING (fMRI/PET) STUDIES ON EMOTION AND AFFECTIVE STYLES

1. CLASSICAL FEAR CONDITIONING

Classical or Pavlovian conditioning (Pavlov, 1927) is a form of associative learning involving a relationship between a neutral event and an event with biological significance, and thus contains elements of both memory and emotional processing (Hugdahl, 1995 for review). In classical conditioning, the neutral stimulus becomes behaviorally significant by being temporally coupled with a salient unconditioned stimulus. Several neuroimaging studies have investigated the neural substrates of classical conditioning. In this paradigm, three experimental phases are usually distinguished. In a habituation, or pre-conditioning phase, emotionally neutral stimuli are presented without additional intervening variables. During the acquisition, or conditioning phase, initially neutral stimuli (conditioned stimuli, CS) become behaviorally salient (CS+) because of temporal pairing with an aversive unconditioned stimulus (US). In the extinction, or post-conditioning phase, the CS+ is presented without US.

In one of the first PET studies of classical fear conditioning Hugdahl and coworkers (Hugdahl et al., 1995) scanned subjects during a habituation and extinction phase, where auditory tones (CS) were presented alone. Between these two phases, the subjects were conditioned to the tones by pairing them with electric shocks (US). The results showed a pattern of right-lateralized activation involving the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (PFC), inferior and superior frontal cortices, inferior and middle temporal cortices.

In a later PET study, Morris et al. (1997) used a differential classical conditioning paradigm using facial expressions as CS and an aversive burst of white-noise as US. During the

extinction phase, the CS+ elicited stronger right-lateralized activation than the CS- in the pulvinar nucleus of the thalamus, OFC (Brodmann areas 10, BA10; Brodmann, 1909), superior frontal gyrus (BA46), and anterolateral thalamus. Furthermore, activation in the right amygdala, the right basal forebrain, right hippocampal gyrus and the bilateral fusiform gyrus was significantly correlated with the CS+-modulated activity in the right pulvinar.

In a follow-up study, Morris and coworkers (Morris et al., 1998a) investigated brain regions showing learning-related modulation in the auditory cortex as a consequence of conditioning. When auditory CS (tones, 200 Hz and 8000 Hz) previously paired with an aversive noise burst (US) were presented alone, learning-modulated activity was observed in the auditory cortex. Regression analyses indicated that conditioned activity within the auditory cortex (bilateral transverse temporal gyrus) covaried with activity in the amygdalae, basal forebrain, and right OFC (and to a lesser extent in the anterior insula and anterior cingulate cortex, ACC).

In a later $H_2{}^{15}O$ PET study, Morris et al. (1998b) used a backward masking procedure to present the CS+ (an angry face previously paired with a burst of white noise) and CS- (another angry face never paired with the noise) below the level of conscious awareness. Whereas the left amygdala was activated when the CS+ was presented above the level of awareness, right amygdalar activation was observed when the CS+ was presented below the level of conscious awareness. Although the authors formally tested the Masking X Hemisphere interaction, the amygdalar activation for masked (medial and inferior) and unmasked (superior and posterior) stimuli was rather different. In fact, the voxels in the left (x = -16, y = -8, z = -14) and right (x = 18, y = -2, z = -28) amygdala were displaced by 15.36mm (Euclidean distance).

Summary

The data on conditioning implicates both PFC and amygdala in associative learning. First it should be noted that the extant studies that have reported asymmetric effects have all been performed with aversive learning paradigms. It will be important in the future to examine appetitive learning to determine if the effects that have been reported for the aversive context are different during appetitive learning. Second, it is difficult to disentangle the active inhibitory processes that are presumably occurring during extinction from the CS-elicited emotional response prior to complete extinction. This makes the pattern of neural activity during extinction particularly difficult to interpret. Despite these caveats, several generalizations can be offered. During extinction in aversive conditioning, the CS+ has been found to elicit greater right-sided activation in several PFC regions including the superior frontal gyrus and the OFC. In addition, some evidence indicates activation of the amygdala. The Morris et al. (1998b) study reported asymmetric differences in amygdala activation in response to masked versus unmasked CS+'s, with the former associated with greater right amygdala activation compared with the latter. However, these asymmetric effects in the amygdala were not in homologous regions.

With the sole exception of the Morris et al. (1998b) study, the other studies of conditioning where asymmetric effects were reported did not rigorously evaluate the Condition X Hemisphere interactions. The lack of formal interaction testing precludes definitive conclusions to be drawn about asymmetric effects that distinguish between conditions. Finally, careful study of the differences between the acquisition and extinction phases are required before concluding that activations observed are associated with emotional effects of CS presentations versus the active inhibitory mechanisms of extinction.

2. REWARD AND PUNISHMENT PROCESSING

Reward and punishment are crucial variables for the regulation of behavior. Reward is associated with approach behavior, acts as positive reinforcer (i.e., increases and maintains the occurrence of behavior that leads to reward), and typically triggers pleasure feelings. Animal studies have stressed the role of the basal ganglia (ventral striatum, particularly the nucleus accumbens and ventral pallidum), OFC, and dorsolateral PFC in reward processing. For example, in animals, neurons in the ventral striatum are activated before an expected reward, suggesting that they may encode reward representation (for a review, Schultz et al., 2000). Human lesion and invasive animal data suggest that the ventral OFC is crucial for monitoring of response-outcome relations (for review, Rolls 2000), especially when reversal learning and extinction are involved. Despite the extensive study of the neural substrates of reward processing in animals, it is in only recent years that the neural activation associated with reward and punishment processing has been studied in the human brain.

In 1997, Thut and coworkers (Thut et al., 1997) published the first human neuroimaging study aimed at investigating brain structures involved in reward processing. $H_2{}^{15}O$ PET scans were obtained while subjects performed a pre-learned delayed go-nogo task, in which abstract shapes predicted the occurrence of a go (speeded key press) or nogo trial (no key press). Abstract (the word "OK") or monetary reinforcement was given if their reaction time was under a given limit. Compared to the abstract reinforcement, monetary reinforcement elicited stronger activation in the dorsolateral PFC (BA10/44), OFC (BA47), thalamus, and midbrain, all in the left hemisphere. Thus, these results highlight a pivotal role for left-sided activation of the OFC and PFC in directing voluntary behavior toward appetitive goals.

Using ^{11}C-labelled raclopride and PET, Koepp et al. (1998) assessed changes in levels of extracellular dopamine while subjects were engaged in a goal-directed video game with monetary incentive. Compared to a control scan, playing the video game was associated with reduced raclopride binding in the striatum, reflecting increased release and binding of dopamine to its receptors. Highlighting the role of the striatum in goal-directed behavior, binding reduction in the striatum (especially left ventral) was positively correlated with task performance. Since the ventral (but not dorsal) striatum receives important projections from the OFC, amygdala, and ACC, the association between ventral striatum and task performance may suggest that the dopamine changes were related to affective components of the task.

Using a computerized gambling task and $H_2{}^{15}O$ PET, Rogers and colleagues (Rogers et al., 1999) explored brain regions involved in deciding between a choice associated with unlikely, yet larger reward or punishment and likely, yet smaller rewards or punishments. Thus, in the former condition, despite the presence of large potential rewards, the opportunity for large potential punishments was also present. Results showed a strongly asymmetric pattern in frontal regions. Whereas increased regional cerebral blood flow (rCBF) during decision-making was observed in several regions of the right PFC - inferior and orbital PFC (BA11), middle frontal gyrus (BA10/11), orbital gyrus (BA11), and inferior frontal gyrus (BA47) - decreased rCBF was observed in, among other regions, the left medial frontal gyrus (BA10).

Recently, Delgado et al. (2000) also explored the neural substrates underlying feedback in a gambling task. Subjects were scanned while were presented with a card with a hidden number that needed to be guessed ("smaller or greater than a given threshold?"). Using an event-related fMRI design, reward trials (win of money), neutral trials, and punishment trials (loss of money) were alternated. In agreement with prior animal work, this study confirmed a primary role of striatal regions in response to reward-related information: correct guesses elicited more sustained

and slowly decaying bilateral activation in the dorsal striatum (caudate) and left medial temporal lobe compared to incorrectly and thus punished guesses. The left-lateralized effect confirmed prior findings of greater involvement of left regions in reward-related information in similar tasks (Koepp et al., 1998; Thut et al., 1997; Zalla et al., 2000).

Employing fMRI and a simple reaction time embedded in a fictitious but engaging competitive tournament, Zalla et al. (2000) explored the role of the amygdala and other regions in processing "winning" or "losing" information. For the subjects, winning and losing depended on the response speed in a cued reaction time task (in reality, winning and losing were parametrically varied independently from subjects' performance). Results showed a laterality effect in the amygdalae: whereas the left amygdala was associated with parametric increases in winning, the right amygdala was associated with parametric increases in losing. Further, winning was associated with increased activation in the left inferior frontal gyrus (BA44), left hippocampus, and right OFC (BA47). Conversely, losing elicited increased activation in three right hemispheric regions: PFC (BA9), putamen, and globus pallidum. Besides confirming a stronger involvement of left and right (especially frontal) regions in approach- and withdrawal-related states, this study showed, for the first time in the intact human brain, an involvement of the left amygdala in reward-related information.

Using a pre-learned delayed pattern recognition task and $H_2{}^{15}O$ PET, Künig et al (2000) compared brain activation in Parkinson patients and control subjects. Subjects were engaged in a matched-to-sample task involving three reinforcement conditions depending on subjects' performance: positive symbolic ("OK") reinforcement, monetary reinforcement and no reinforcement (nonsense feedback). In controls, both positive reinforcements elicited bilateral activation in the ACC (BA24) and caudate as well as activation in the left cerebellum, and left medial frontal gyrus; monetary rewards additionally elicited bilateral striatal activation and left

midbrain activation. Further, general processing of positive reinforcements involved additional left hemispheric regions, the inferior parietal gyrus (BA40) and medial temporal gyrus (BA21). These results confirm (a) an important role of dopaminergic mesostriatal/mesocorticolimbic and dorsolateral PFC regions in reward processing, and (b) a left hemispheric preponderance in such processes.

Recently, O'Doherty and colleagues (2001a) further explored the role of the human OFC in abstract representations of reward and punishment. Subjects performed a visual reversal-learning task, in which they attempted to determine by trial-and-error which of two stimuli was linked to (fictive) reward or punishment (stimulus-reinforcement contingencies were probabilistically determined). Results suggested a striking dissociation within the OFC with respect to reward or punishment: whereas the medial (bilateral) OFC was involved in reward outcomes, the right lateral OFC (BA10/11) was implicated in punishment outcomes. Further, correlational analyses revealed an asymmetrical pattern in the OFC: the left medial and right lateral OFC were positively correlated with reward and punishment magnitude, respectively.

Summary

The findings reviewed in this section are consistent with earlier electrophysiological findings that suggest asymmetric activation in regions of the PFC that differentiate between reward and punishment and approach- and withdrawal-related emotion (Davidson, 2000; Davidson et al., 2000a for reviews). Moreover, the neuroimaging data permit more specific and differentiated anatomical specification and indicate that asymmetries are observed in both orbital/ventral and dorsolateral regions of the PFC. Results from O'Doherty et al. (2001a) suggest that medial territories in the OFC may crucially involved in reward outcomes, whereas lateral (possibly right) OFC (BA10/11) may be more involved in punishment outcomes. In

addition, the neuroimaging data suggest that asymmetries may also be present in the amygdala. Although, replication of this laterality effects is warranted, it is interesting to note that in rodents there is evidence suggesting a predominant role of the right than left amygdala in memory consolidation for aversive experiences (Coleman-Mesches and McGaugh, 1995a,b).

Two cautions require explicit mention in considering this literature. First, in addition to the asymmetric patterns of activation highlighted above, there often were other bilateral activations present in response to the incentive conditions that were studied. Thus, the asymmetry effects should be considered as a matter of degree and not in any absolute fashion. Moreover, these findings should be placed within an overall circuit that may include both bilateral and asymmetric effects. Second, many of the studies did not formally test the Condition X Hemisphere interactions. Thus it is not always possible to know if the particular asymmetric finding that is reported is significantly greater for one hemisphere region compared with the other. The few studies where explicit tests for asymmetry were conducted have been noted.

3. EXTERNALLY ELICITED AFFECT

In 1996, our laboratory published the first report of amygdalar activation in response to complex aversive visual stimuli (Irwin et al., 1996). In this study, three coronal sliced were acquired while female participants viewed alternating blocks of aversive and neutral complex pictures from the International Affective Picture Series (IAPS; Lang et al., 1995). When contrasting the BOLD (blood oxygen level-dependent) signal between neutral and negative pictures, bilateral amygdalar activation emerged during the latter condition.

In a series of influential PET studies, Lane, Reiman and coworkers investigated several aspects of the functional neuroanatomy of affect including the manner in which affect was elicited (internally generated versus elicited by external stimuli; Reiman et al., 1997) and the impact of differential attentional focus toward the affective state (Lane et al., 1997a). In a first study, Reiman et al. (1997) contrasted film- and recall-generated emotion, without considering the valence or discrete emotion involved (happiness, sadness, disgust). Film-generated emotion elicited stronger activation in bilateral occipitotemporoparietal regions, lateral cerebellum, hypothalamus, anterior temporal cortex, amygdala and hippocampus; and recall-generated emotion induced stronger activation in the anterior insula. There were no pronounced asymmetric effects in these studies.

The main goal of the fMRI study by Canli and coworkers (Canli et al., 1998) was to explicitly test the laterality-valence hypothesis. The task involved presentation of positively and negatively valenced pictures. For those subjects who rated the positive and negative pictures comparably in arousal, greater left-hemispheric activity for positive than negative affective pictures was observed in middle frontal (BA6/8) and middle/superior temporal (BA21/38) structures. Conversely, compared to positive, negative pictures elicited greater right-hemispheric activation in inferior frontal PFC.

Using a fMRI protocol with coverage limited to occipital and occipito-parietal regions, Lang et al. (1998) explored the role of the visual cortex in processing emotional and neutral IAPS pictures. Both pleasant and unpleasant pictures elicited spatially larger activation in bilateral occipito-parietal, and especially occipital, regions. Aversive pictures specifically activated right parietal regions and right BA18, whereas pleasant pictures were associated with larger activation in the left fusiform and right lingual gyrus.

In a study that effectively exploited an ideographic approach to the elicitation of positive, approach-related emotion, Bartels and Zeki (2000) scanned 17 subjects while they observed photographs of the loved one and friends. Presentation of partner's face was accompanied by positive affect and increased arousal, as assessed in separate psychophysiological sessions. The results showed a pattern of asymmetrical effects. Perception of the loved person was associated with activation in various subcortical and paralimbic regions in the left hemisphere (middle insula, head of the caudate nucleus, putamen) as well as bilateral activation in the ACC (BA24) and posterior hippocampus. *De*activations (friends > partner) were observed in several right-sided regions: PFC (BA9/46), parietal (BA39/19), middle temporal cortex (BA21/22), and posterior cingulate gyrus (BA23/29/30) as well as medial PFC (BA9) and left posterior amygdaloid region.

In a recent study, Kawasaki, Adolphs, Damasio and colleagues (Kawasaki et al., 2001) recorded single-unit responses to aversive pictures in the right ventral PFC of a patient implanted for diagnostic purposes. Results showed selective responses to aversive stimuli in the right PFC between 120-160 ms, suggesting that the PFC can provide rapid (and likely coarse) categorization of emotional information.

A number of studies have used auditory stimuli to elicit emotion while measures of brain function were examined with PET or fMRI. Lorberbaum and coworkers (Lorberbaum et al., 1999) scanned mothers while they heard cries of unfamiliar infants, which elicited more sadness and urge to help than a control sound (white noise). Based on prior animal work postulating the cingulate cortex in maternal behavior (Maclean, 1990; Devinsky et al., 1995), the authors hypothesized a primary role of this brain region during exposure to infant cries. Compared to the control sounds, infant cries were indeed associated with increased fMRI signal in the subgenual ACC extending to the medial PFC and superior frontal gyrus, all in the right hemisphere. Right PFC involvement in this mildly distressing situation is consistent with the approach-withdrawal

model (Davidson, 2000). However, since no control emotional condition was used, it is unclear whether right ACC and PFC activation were linked to valence per se, unspecific arousal, or attention-engaging mechanisms present in the infant cry condition.

Based on the observation that music can be a potent emotional elicitor, Blood et al. (1999) used unfamiliar music passages manipulated in their degree of dissonance to study the neural correlates of affective responses to music. Increasing dissonance was positively correlated with rCBF in the right parahippocampal gyrus (BA28/36) and right precuneus (BA7), and negatively correlated with rCBF in the OFC (bilateral, BA13/14), subcallosal ACC (BA25), and right frontal polar cortex (BA10). Similarly, unpleasantness ratings were positively correlated with activity in the right parahippocampal region as well as in the posterior cingulate cortex (BA23/31), and negatively correlated with rCBF in the right OFC and medial subcallosal ACC.

In a recent event-related fMRI study, Goel and Dolan (2001) explored the brain substrates of humor by presenting semantic and phonological jokes. When comparing funny to non-funny jokes (both, semantic and phonological), the former were associated with stronger activation in the medial ventral PFC (BA10/11). In this region, pleasantness ratings of the jokes were positively correlated with the BOLD signal. Thus, these results suggest that positively-valenced auditorily presented affective information activates regions associated with reward representation (Rolls, 2000).

Olfactory stimuli involve a strong hedonic component (pleasant vs. unpleasant), and are thus ideal for eliciting approach and withdrawal tendencies in both animal and humans. In one of the first neuroimaging studies using emotionally charged olfactory stimuli, Zatorre et al. (1992) reported right OFC activation during exposure to pleasant, neutral and aversive olfactory stimuli. A series of subsequent PET and fMRI studies have been conducted to examine patterns of regional brain activity during pleasant and unpleasant odorant stimulation (e.g., Zald & Pardo,

1997; Zatorre et al., 2000; O'Doherty et al., 2000). These studies have not found systematic variations in the asymmetry of activation produced by stimuli of different valences. What does appear to be similar across all of these studies is activation of regions of OFC. This common focus of activation is likely a consequence of two factors. First is the suggestion that OFC represents a brain region for primary olfactory processing (see Rolls, 1999 for review). And second, OFC activation has been hypothesized to occur during reversal learning (e.g., Rolls, 2000). In response to olfactory stimuli, it is frequently observed that the hedonic valence of the stimulus to which an individual is exposed changes rapidly over time. Thus, the OFC is likely to be activated in such circumstances. The rapidly changing hedonic nature of olfactory stimuli also may account for some of the variability in the findings of studies that have attempted to contrast pleasant and unpleasant odors.

In a recent fMRI study, O'Doherty et al. (2001b) investigated the role of the OFC and amygdala during presentation of both pleasant (glucose) and aversive (salt) tastes. Compared to neutral, both pleasant and aversive taste elicited stronger bilateral activation in the amygdala, OFC, and insula/frontal operculum. Within the OFC there were both overlapping and unique regions of activation for the two valences (the aversive condition elicited slightly more medial OFC activation). Whereas these results confirmed that both pleasant and unpleasant tastes are represented in the OFC, amygdalar activation in response to the glucose condition implies that the amygdala activates to both aversive and appetitive stimuli. Direct contrasts between the pleasant and unpleasant taste conditions were not performed and thus we cannot evaluate whether activation in the amygdala was greater for unpleasant compared with pleasant stimuli.

In an event-related fMRI study, Critchley and colleagues (Critchley et al., 2001) investigated brain activation during outcome anticipation in a two-choice decision-making task associated with monetary reward or punishment. The independent variable of interests where the

degree of uncertainty (parametrically varied) and autonomic arousal (indexed via online SCR recording). During the anticipatory period (pre-feedback), the strongest foci of activation were in the right OFC and anterior insula. What was of particular interest in this report was the association observed between activation of the right dorsolateral PFC and right ACC and electrodermal activity.

Summary

Most of the studies reviewed in this section involved the presentation of visual emotional stimuli, typically film clips or pictures. One of the methodological conundrums of research on emotion is that laboratory environments are typically not places where strong emotions are expected to occur and thus, efforts to elicit such emotion in subjects may be thwarted by regulatory strategies invoked by subjects to attenuate the magnitude of the elicited affect. Oftentimes these regulatory maneuvers are generated non-consciously. Thus, the activations that are observed during such experiments may reflect an unknown mixture of processes associated with the generation of emotion as well as with the regulation of that emotion. Note, for example, that the often-reported ACC activation in studies eliciting affect may be partially due to such regulatory processes.

Some of the studies reviewed in this section did not find reliable asymmetric effects in response to externally-elicited emotion. In the experiments of the Arizona group (Reiman et al., 1997; Lane et al., 1997b), both cortical and limbic regions were activated but not asymmetrically. The relatively diffuse pattern of activation found in these studies may reflect the complex nature of the emotions that were produced by the film clips using by these investigators to provoke emotion. These are complex film clips that produce a differentiated range of emotional changes over the course of the film clip. In earlier work conducted in our laboratory using film-clips as

elicitors and brain electrical activity measures to make inferences about regional brain activation, we too found that examining the data across the entire length of a short film clip (i.e., two minutes), no reliable asymmetries were observed (Davidson et al., 1990). It was only when we extracted very short epochs (on the order of a few seconds) of brain electrical activity that were coincident with objectively coded facial expressions of emotion that systematic asymmetrical effects were observed. Unfortunately, this was not possible using PET since the data were averaged across approximately two minutes of the film clip. Using event-related fMRI and objective peripheral measures of emotion induction (e.g., skin conductance measures), other investigators have reported robust asymmetric effects (e.g., Critchley et al., 2001). Canli et al. (1998) also found that for subjects who rated positive and negative pictures comparably in arousal, asymmetric fMRI signal changes were observed with greater right-sided activation in the inferior frontal PFC in response to negative compared with positive pictures.

The use of briefer stimuli in the visual modality, including ideographically chosen stimuli (as in Bartels & Zeki, 2000) was associated with more consistent asymmetric effects compared with longer duration film clips, with the exception of stimuli whose repetitive presentation changes their hedonic value. Olfactory and gustatory stimuli are an example of this latter type where rapid changes over time in hedonic effects may produce complex and difficult to interpret patterns of activation. Affective acoustic stimuli such as infant cries have been found to produce strong right-lateralized changes. It may be easier to elicit stronger emotion in the auditory modality compared with the visual modality. Finally, the use of reward and punishment contingencies, as described in the earlier section, may be particularly promising and can be usefully be exploited using event-related fMRI paradigms. The strong associations reported between the magnitude of electrodermal changes and right PFC activations in the recent report by Crithley et al. (2001) needs to be replicated and examined further. These findings also suggest

that it is particularly for those subjects showing strong autonomic changes that these right-sided activations are apparent. These data indicate that the mere presentation of particular incentives is insufficient to guarantee an emotional response. It may only be for that subset of subjects showing objective signs of emotion that lateralized activations of the type described are found.

IV. CONCLUSION

This chapter presented a selective review of recent PET and fMRI studies on human emotion that have reported lateralized activations. In general, where such lateralized changes have been reported, they are most often supportive of the approach-withdrawal framework articulated in a series of publications by Davidson and his colleagues (e.g., Davidson, 1998; Davidson, 2000; Davidson et al., 2000a). However, it is also apparent that lateralized PFC changes associated with approach and withdrawal-related emotion are not consistently obtained. The inconsistencies in the literature are likely a function of a multitude of causes including methodological issues in the statistical assessment of asymmetry, variability in affective responses that are elicited by particular stimulus conditions and the failure to utilize proper control conditions in the experiments. Having said this, it must also be noted that when asymmetries are observed, they are a matter of degree and are by no means absolute. Moreover, the PFC is part of a more complex circuit that includes other cortical and subcortical zones interconnected with the PFC. It is conceivable that similar emotional states can arise as a consequence of somewhat different patterns of activation within this circuitry and that the differences among these emotional states may only be discovered with more precise and detailed probing of the cognitive, attentional, memory and motor changes associated with these emotional

variants. For a detailed discussion of the functional and evolutionary significance and origins of these asymmetries associated with emotion, the interested reader can consult recent reviews by Davidson (Davidson, 2000; Davidson et al., 2000a).

The data on amygdala asymmetries are complex and also not entirely consistent. Where studies have examined relations between activation in the left and right amygdala and measures of negative affect, they more often than would be expected by chance report stronger associations with the right amygdala than with the left amygdala. The Morris et al. (1998b) study is the only one to suggest that the right amygdala is preferentially involved in the processing of non-conscious information while the left amygdala is involved in the processing of conscious emotional information. Zalla et al. (2000) suggest that the left amygdala is involved in reward and appetitive processing while the right amygdala is more involved in punishment and aversive processing. These claims all require systematic replication.

It is clear that research on asymmetrical activations in hemodynamic neuroimaging research is still very much in its infancy and there are many methodological and conceptual problems to resolve in the future. The availability of these methods will enable investigators to systemically examine both cortical and subcortical asymmetries with a level of spatial and temporal precision not previously available. This bodes well for resolving some of these problems in the future.

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