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EXPERIENCE-DEPENDENT CHANGES IN HUMAN BRAIN ACTIVATION DURING CONTINGENCY LEARNING

M. W. SCHLUND* AND D. ORTU

Department of Behavior Analysis, University of North Texas, Denton, TX, USA

Abstract—Successful adaption requires learning to respond appropriately to cues associated with response-reinforcer contingencies. In this investigation, we used functional magnetic resonance imaging to characterize changes in frontal and limbic activation associated with learning under a positive reinforcement contingency. Imaging analyses identified linear and nonlinear changes in brain activation across nine reinforcement trials when response accuracy and reaction times were stable. The development of contingency control was generally associated with linear increases or inverted-U shaped changes in activation in superior, medial and orbitofrontal (OFC) regions, amygdala, insula and the medial temporal lobe. Linear decreases and U-shaped changes in activation were generally observed in parietal, occipital and cerebellar regions. Results highlighting linear increases in activation in superior, medial and OFC regions suggest involvement in the development of contingency control, even when behavior is stable. Results also highlighted a positive correlation between changes in OFC activation and amygdala activation. However, inspection of the correspondence between group changes and individual subject changes in OFC, amygdala and insula activation revealed that approximately half of subjects exhibited changes resembling group changes and the strength of the OFC-amygdala relationship varied markedly between subjects. Such disparities highlight a unique opportunity for exploring individual differences in regional sensitivity to contingency as well as improving experimental preparations to better highlight and control the effects of extraneous variables. Published by Elsevier Ltd on behalf of IBRO.

Key words: medial frontal, orbitofrontal, amygdala, reward, reinforcement, instrumental learning.

Successful adaptation to an environment requires learning to respond appropriately to cues associated with response-reinforcer contingencies. During the development of contingency control, differential reinforcement produces an increase in contingency appropriate responding and an associated increase in the local rate/density of reinforcement that facilitates stable responding. This process involves a widely distributed network of brain regions that includes medial and orbitofrontal involvement in forming response-outcome relations (Izquierdo et al., 2004; Tanaka et al., 2008), recruitment of anterior cingulate in error detection and associating contextual information with responding (Kerns et al., 2004; Williams et al., 2004; Magno et al., in press), reward processing in striatum, amygdala and insula (Baxter and Murray, 2002; Hommer et al., 2003; Delgado et al., 2005; Magno et al., in press), as well medial temporal lobe involvement in forming relational and associative memories (Eichenbaum and Cohen, 2001; Law et al., 2005). Considerably less is known, however, about the form of regional changes in activation that occur during the development of contingency control. Given that an insensitivity to contingencies is a feature of clinical dysfunction (e.g., Schlund, 2002a,b; Mitchell et al., 2006; Remijnse et al., 2006; Waltz and Gold, 2007), advances in understanding normative levels of regional plasticity may provide new insights into neuropathology (Schlund et al., 2008). Accordingly, this investigation used functional magnetic resonance imaging (fMRI) to characterize changes in brain activation in frontal and limbic regions associated with the development of contingency control.

Several functional neuroimaging investigations involving reinforcement learning have observed that increases in contingency control correlate with increases in medial and orbitofrontal activation. For example, Haruno et al. (2004) observed that increased rates of learning were associated with greater lateral prefrontal and orbitofrontal activation. Law et al. (2005) observed that faster rates of paired-associate learning were correlated with greater activation in the medial frontal gyrus, as well as the hippocampus and parahippocampus. Using a more fine-grained approach, Seger and Cincotta (2006) observed that numerous prefrontal regions showed a steady increase then gradual decline in activation while the hippocampus showed a steady decline then an increase in activation as stable responding emerged over reinforcement trials. Elliott et al. (2000) also reported that "runs" of monetary gains or penalties correlated with increases in activation in lateral orbitofrontal cortex as well as the insula. Schlund et al. (2008) tracked changes in brain activation across five consecutive reinforcement trials and reported incremental increases in activation in the medial frontal gyrus, anterior cingulate and striatum and inverted U shaped changes in the hippocampus and parahippocampus—no significant changes were observed in the amygdala or insula.

While such findings suggest systematic changes in medial frontal and orbitofrontal responses, as well as medial temporal and limbic responses, during the development of contingency control, the functional relationship between cumulative reinforcement and changes in regional activation remains to be isolated. Accordingly, the

*Correspondence to: M. W. Schlund, Department of Behavior Analysis, University of North Texas, P. O. Box 310919, Denton, TX 76203, USA. Tel: +1-940-565-2274.
E-mail address: Michael.Schlund@unt.edu (M. W. Schlund).
Abbreviations: ANOVA, analysis of variance; EPI, echo planar imaging.

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present investigation examined changes in regional activation across nine reinforcement trials under conditions where response accuracy and reinforcement rate were comparable across subjects. We also expanded on our earlier investigation by identifying linear and nonlinear changes in activation and we assessed the level of correspondence between regional changes in activation identified in group analyses with those of individual subjects. While rare within human neuroimaging research, such assessments may provide important insights into the degree of between-subject variability in regional sensitivity to contingency or lay the foundation for examining extraneous variables hypothesized to contribute to between-subject variability.

EXPERIMENTAL PROCEDURES

Seventeen, healthy right-handed adults participated. Subjects reported being between 18 and 50 years of age, right-handed, free of medications affecting the CNS or the autonomic system for at least 2 weeks, and without a personal history of psychiatric disorder. The experiment reported was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of subjects. Formal approvals for the experiment described were obtained from the University of North Texas and University of Texas Southwestern Institutional Review Boards for the Protection of Human Subjects and can be provided upon request.

Subjects performed an instrumental learning task during four consecutive ~8 min neuroimaging sessions. Instructions emphasized the goal of learning how to respond on either of two available buttons depending on the visual stimulus presented and that correct responding would produce money ($0.50 per correct response). Thus, instructions made explicit the relationship between visual stimuli and the presence or absence of monetary reward—no trials involved other kinds of stimulus-outcome relations, such as loss or non-reward for correct responding. The task consisted of solving sixteen discrimination problems (four per imaging session). Each discrimination problem consisted of ten trials with an S+1 visual cue and ten trials with an S+2 visual cue. S+ cues were non-letter ASCII characters that were correlated with a positive reinforcement contingency and were presented in a randomized order. Novel S+ cues were used for each discrimination problem. During a trial, an S+ cue was presented for 7 s (duration jittered 6–8 s), followed by a 2 s "CHOOSE" prompt, during which subjects used their right thumb to press either a left or right response button. Contingency appropriate ("correct") button presses produced the 2 s reinforcer prompt "50 Cents," while "incorrect" button presses or non-responding produced the prompt "0 cents." As expected, correct responses occurred to the first or second presentation of an S+ cue and were maintained over subsequent presentations. After each outcome, a 7 s (duration jittered 6–8 s) intertrial interval cued with a fixation stimulus was presented. Using this design, all subjects rapidly showed contingency appropriate responding that remained stable and experienced nearly identical rates of reinforcement per minute. Between discrimination problems, the correct response button associated with each S+ cue was randomized. However, four of the sixteen discrimination problems had the same response designated as correct for both S+ cues in order to minimize learning both contingencies through deduction (e.g. if the left button does not produce money under S+1, then left presses will produce money under S+2 and right presses will produce money under S+1). Finally, subjects experienced one discrimination problem prior to neuroimaging to become familiar with the stimulus displays, responding and timing of events. Instructions emphasized that compensation for participation included money earned during the task.

Functional MRI images were collected on a 3 T scanner at the Meadows Imaging Research Center located in Dallas Texas. T_1 weighted anatomical volume images were collected for each subject using a MPRAGE sequence with a high-resolution isovoxel acquisition of 1 mm^3. Functional MRI data were gathered using a single shot echo planar imaging (EPI) sequence with a TR of 2.5 s, a TE of 20 ms, a 90 degree flip angle, 64×64 matrix size and field of view 24 cm, yielding voxels measuring 3×3 mm^2 in plane. Forty-three contiguous 3 mm thick sections were obtained. The first two volumes were discarded to allow for equilibration effects. Functional images were first reconstructed from k-space to image space for further processing. Data analysis was performed using SPM 2 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/). Preprocessing procedures included reorientation, slice acquisition time correction, coregistration, within-subject realignment, spatial normalization to the standard Montreal Neurological Institute EPI template with resampling to a 2×2×2 mm^3 voxel size, and spatial smoothing using a Gaussian kernel (6 mm full width at half-maximum). High pass filtering was applied to the time series of EPI images to remove any low frequency drift in EPI signal. A canonical hemodynamic response function was used as a covariate in a general linear model and a parameter estimate, which equates to percent change in the global mean blood-oxygen-level-dependent (BOLD) signal, was generated for each voxel for each event type. The parameter estimate, derived from the mean least squares fit of the model to the data, reflects the strength of covariance between the data and the canonical response function for a given event. Because incorrect responding often occurred on the first presentation of S+ cues, the total number of reinforced trials decreased from 10 per S+ cue to nine. Accordingly, separate parameter estimates were obtained by modeling the hemodynamic response function to the onsets of both S+1 and S+2 on the first reinforced trial, both S+1 and S+2 on the second reinforced trial and continuing to the ninth reinforced trial. Associated reinforcer deliveries were also modeled as covariates of no interest. This approach provided a parameter estimates for each reinforced trial, for each subject, without the need for arbitrary averaging across trials. In the end, a series of nine contrast images for each subject was produced that reflected activation to the S+ cue for the first reinforcement trial through the ninth reinforcement trial.

The series of contrast images were taken to a second-level group analysis that treated intersubject variability as a random effect. Because the focus of the investigation was on identifying experience-dependent BOLD response changes to S+ cues (using only reinforcement trials), we utilized a repeated measures analysis of variance (ANOVA) and separate contrast weight sequences designed to highlight linear increases/decreases and curvilinear (U and inverted U) changes. A voxel-wise threshold of $P \leq 0.001$, uncorrected for multiple comparisons, and 40 contiguous voxels were employed. The location of voxels with significant activation was summarized by their local maxima separated by at least 8 mm, and by converting the maxima coordinates from MNI to Talairach coordinate space using conventional transformations (Lancaster et al., 2007). These coordinates were finally assigned neuroanatomic labels using the Talairach database (http://www.talairach.org/daemon.html) and Talairach atlas (Talairach and Tournoux, 1988). Resulting statistical parametric maps were then overlaid onto a reference brain using MRIcron software (http://www.sph.sc.edu/comd/rorden/mricron/).

RESULTS

An a priori paired-sample *t*-test revealed a significant increase in response accuracy from trial 1 (M=48.57, SD=12.97) to trial 2 (M=96.73, SD=8.58); $t(16)=11.12$,

$P<0.001$. This finding also reveals that the development of contingency control was associated with an increase in reinforcement rate. Repeated measures ANOVA revealed no significant change in response accuracy across trials 2 through 10 ($F(8,16)=0.94$; $P=0.49$), which averaged 98.1% (SD=1.13) and that reinforcement rates remained stable. No significant change in reaction time across trials 1 through 10 was observed ($F(9,16)=0.42$; $P=0.92$). Between the first eight and last eight blocks of discrimination problems, there were no significant differences in accuracy (as well as reinforcement rates) across trials 2–10 ($F(8,16)=1.89$; $P=0.07$) or in reaction time ($F(8,16)=1.36$; $P=0.22$). In sum, accurate responding emerged by the second trial and then accuracy and reinforcement rates remained stable through the tenth trial. The absence of changes in response accuracy and reaction time over trials and imaging runs reduces the likelihood these variables could function as confounds in the imaging analyses.

Fig. 1 and Tables 1 and 2 present results of the repeated measures ANOVA used to identify the form of significant regional BOLD response changes to S+ cues on the first reinforcement trial through the ninth reinforcement trial. Regional changes were not limited to linear increases and decreases but included curvilinear (U and inverted-U shaped) changes. Generally, frontal, temporal and limbic regions implicated in behavioral regulation, positive reinforcement learning and reward processing, such as the left amygdala and orbital, medial and superior frontal regions ($z=-10$ to $z=+37$), evidenced linear increases. However, increases were also noted in areas of the precuneus and lingual/fusiform gyri. Increases followed by decreases in activation were observed in the insula, left parahippocampus and posterior parietal regions. Regions associated with visual-spatial mapping, vision and recognition memory such as the fusiform gyrus and superior and inferior parietal lobules showed pronounced linear decreases, while other related regions such as the precuneus and lingual gyrus showed an initial decline followed by subtle increases. A similar decline and rise in the BOLD response was also observed in the cerebellum.

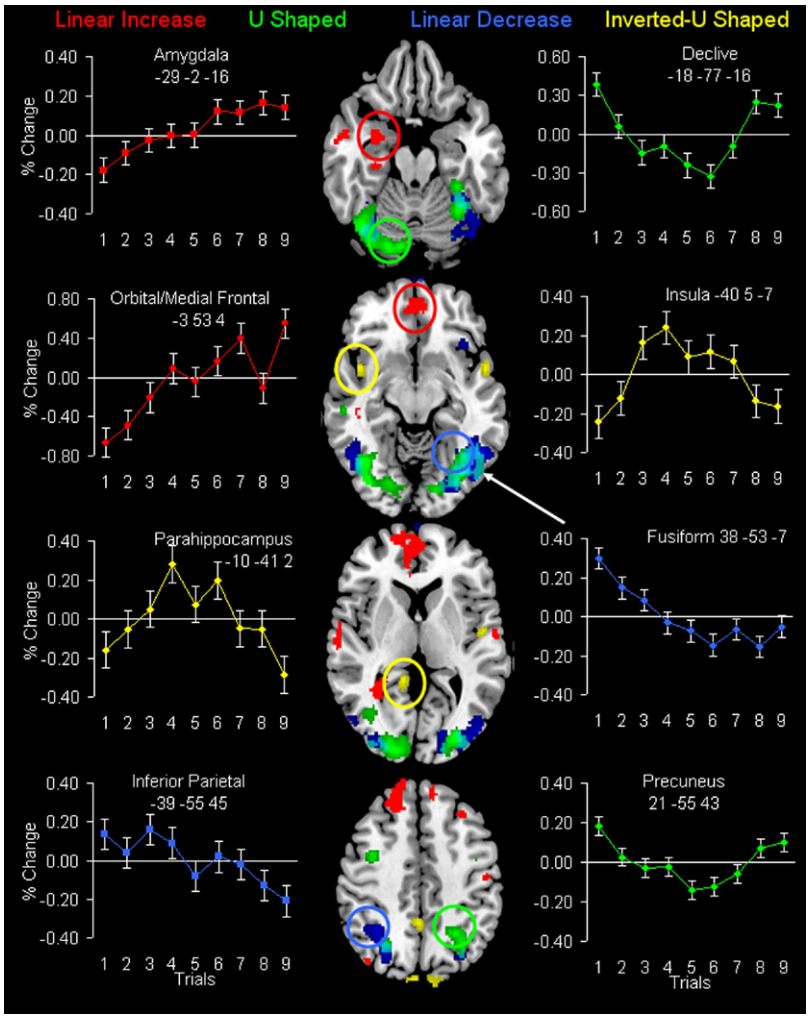

Fig. 1. Group regional changes in activation to consecutive S+ cue presentations. Activation maps highlight regions that exhibited significant BOLD response increases (linear=red; inverted-U shaped=yellow) and decreases (linear=blue; U-shaped=green) across trials containing correct responses. Plots show changes in the percentage of global mean intensity beginning with the first reinforced trial (either trial 1 or 2) and ending with the ninth reinforced trial. Results are shown in neurological convention.

Table 1. BOLD response changes to S+ cues (thresholds $P \leq 0.001$, k=40)

Region	Cluster Size	X	Y	Z	Voxel T
Linear increase					
Left					
Medial frontal gyrus	(2132)	−3	53	4	5.48
Superior frontal gyrus	(2132)	−20	30	46	5.41
Middle temporal gyrus	247	−46	−73	24	5.35
Posterior cingulate	271	−9	−57	15	5.15
Amygdala	155	−29	−2	−16	4.82
Lingual/fusiform gyrus	227	−31	−48	1	4.67
Superior temporal gyrus	81	−58	−13	4	4.46
Precentral gyrus	86	−51	−6	26	4.19
Hippo/parahippocampus	44	−27	−21	−14	4.14
Precuneus	(271)	−3	−60	22	3.83
Superior occipital gyrus	(247)	−33	−85	30	3.69
Right					
Superior frontal gyrus	2132	6	50	27	6.49
Superior temporal gyrus	130	40	18	−22	5.57
Cuneus	43	23	−74	7	5.08
Transverse temporal gyrus	70	56	−18	11	4.62
Inferior frontal gyrus	(130)	34	15	−17	4.22
Insula	117	45	−11	22	3.92
Precentral gyrus	55	45	−19	41	3.85
Orbitofrontal	(2132)	6	50	−10	3.45
Postcentral gyrus	(55)	50	−18	32	3.32
Inverted U					
Left					
Insula	53	−40	5	−7	4.28
Parahippocampus	76	−10	−41	2	4.26
Cingulate gyrus	55	−4	−49	41	4.09
Cuneus	183	−5	−86	36	3.84
Precuneus	117	0	−68	25	3.72
Right					
Postcentral gyrus	91	18	−47	63	4.42
Superior temporal gyrus	55	49	4	−3	4.2
Insula	182	45	−8	8	3.85
Posterior cingulate	(117)	6	−56	24	3.29
Precuneus	(183)	13	−84	42	3.19

Regions in parentheses highlight secondary local maxima.

The correspondence between the form of group BOLD response changes and individual subject changes was also examined. Fig. 2 shows response profiles of the orbital frontal gyrus, amygdala, insula and parahippocampus for each subject. These regions were selected because of their various roles in the development of contingency control. In particular, the orbital frontal cortex has been implicated in the representation of reward information (e.g., Rolls, 2004), and along with the amygdala and insula have been found to respond to rewards and reward cues (Baxter and Murray, 2002; Hommer et al., 2003; Magno et al., in press; Hirai et al., 2009) as well as show sensitivity to increases in the local density of rewards and penalties (Elliott et al., 2000). For each region (column), the first row of plots highlights the number of subjects that showed linear increases in activation, the second row of plots highlights the number of subjects showing no change in activation and the third row of plots highlights the number of subjects showing curvilinear (U and inverted-U shaped) changes in activation. For clarity, red outlined plots highlight the regional response profile identified in the group analysis and presented in Fig. 1. Fig. 2 reveals that for each brain region, approximately 50% of subjects exhibited response profiles that were consistent with changes identified by the group analyses.

The relationship between OFC and amygdala activation at a group and individual subject level was also examined given the working relationship between these regions in behavioral regulation (Schoenbaum et al., 2003; Ridderinkhof et al., 2004; Schoenbaum and Roesch, 2005; Dolan, 2007), and especially in response selection determined by outcomes (Izquierdo et al., 2004). Results of a regression analysis (Fig. 3, left plot) performed between S+ cue related activation, across trials, in the left orbital frontal region and the amygdala revealed a significant but low positive correlation ($r=0.23$; $P<0.005$). The right plot presents individual subject correlations rank ordered by magnitude. Results highlight considerable between subject variability in the strength of OFC-amygdala synchronicity, with some subjects falling in the moderate to high range and others showing a weak or negative association.

Table 2. BOLD response changes to S+ cues (thresholds $P \leq 0.001$, k=40)

Region	Cluster Size	X	Y	Z	Voxel T
Linear decrease					
Left					
Corpus callosum	44	1	−11	25	4.46
Superior parietal lobule	924	−33	−66	46	6.31
Inferior occipital gyrus	893	−31	−84	−4	5.52
Inferior parietal lobule	(924)	−39	−55	45	4.67
Declive	257	−32	−65	−20	4.32
Right					
Fusiform gyrus	2079	38	−53	−7	5.97
Middle occipital gyrus	(2079)	41	−72	−7	5.78
Insula	53	40	9	4	4.2
Superior parietal lobule	97	32	−57	46	4.16
Lingual gyrus	77	17	−78	−1	4.15
Inferior parietal lobule	203	48	−42	52	4.09
Postcentral gyrus	(203)	56	−36	49	3.89
Superior parietal lobule	190	24	−72	45	3.74
Insula	43	32	19	−1	3.53
U-shaped					
Left					
Declive	5003	−18	−77	−16	6.7
Precentral gyrus	626	−26	−25	50	5.03
Postcentral gyrus	(626)	−41	−24	63	4.65
Middle temporal gyrus	136	−51	−21	−4	4.48
Insula	52	−48	−22	21	4.41
Precuneus	126	−26	−63	37	4.11
Superior parietal lobule	(126)	−24	−70	44	4.08
Middle frontal gyrus	61	−35	32	30	3.75
Inferior parietal lobule	(52)	−53	−23	28	3.12
Right					
Lingual gyrus	(5003)	23	−85	6	6.69
Cuneus	(5003)	21	−94	7	6.12
Precuneus	703	21	−55	43	5.75
Precentral gyrus	105	32	−10	51	4.37
Cingulate gyrus	91	2	−17	30	4.25

Regions in parentheses highlight secondary local maxima.

DISCUSSION

Results of the present investigation highlighted widespread changes in regional activation associated with the development of contingency control. While declines in activation are commonly observed during learning and with increased experience (Chein and Schneider, 2005; Delgado et al., 2005; Takashima et al., 2006), results of the present investigation highlighted both linear and non-linear increases and decreases in activation when analyses targeted trial-by-trial changes. During the development of contingency control we generally observed both linear and inverted-U shaped changes in frontal, limbic and medial temporal lobe regions and linear decreases and U shaped changes in parietal, occipital and cerebellar regions. These findings reinforce applications of functional magnetic resonance imaging to gain insights into regional plasticity and highlight dynamic changes among brain regions within a network (Poldrack et al., 2001; Doyon et al., 2002; Haruno et al., 2004; Law et al., 2005).

Our results highlighting significant change in superior, medial and orbitofrontal regions are consistent with results of prior investigations that have observed a positive correlation between activation and rates of learning and increases in activation across reinforcement trials (Haruno et al., 2004; Law et al., 2005; Seger and Cincotta, 2006). However, one significant difference relative to prior investigation is that our findings related changes in S+ cue activation directly to consecutive reinforcer presentations. Consequently, the contributions of any between-subject differences in performance accuracy or reinforcement rate were minimized. The linear increases in activation over reinforcement trials suggest superior, medial and orbitofrontal regions may play a role in discriminating contingency and each successive reinforcer enhances neural activity. The response profile also illustrates that within these frontal regions contingency control develops incrementally even when response accuracy and reaction time remain stable. A similar escalation in activation to the S+ cue over reinforcement trials was observed in the amygdala, which is consistent with hypothesized frontal-amygdala interactions in behavioral regulation (e.g., Dolan, 2007). The escalation in amygdala activation also suggests the rate of regional change is a function of the number of reinforcer deliveries. In contrast to the linear increases observed in frontal and amyg-

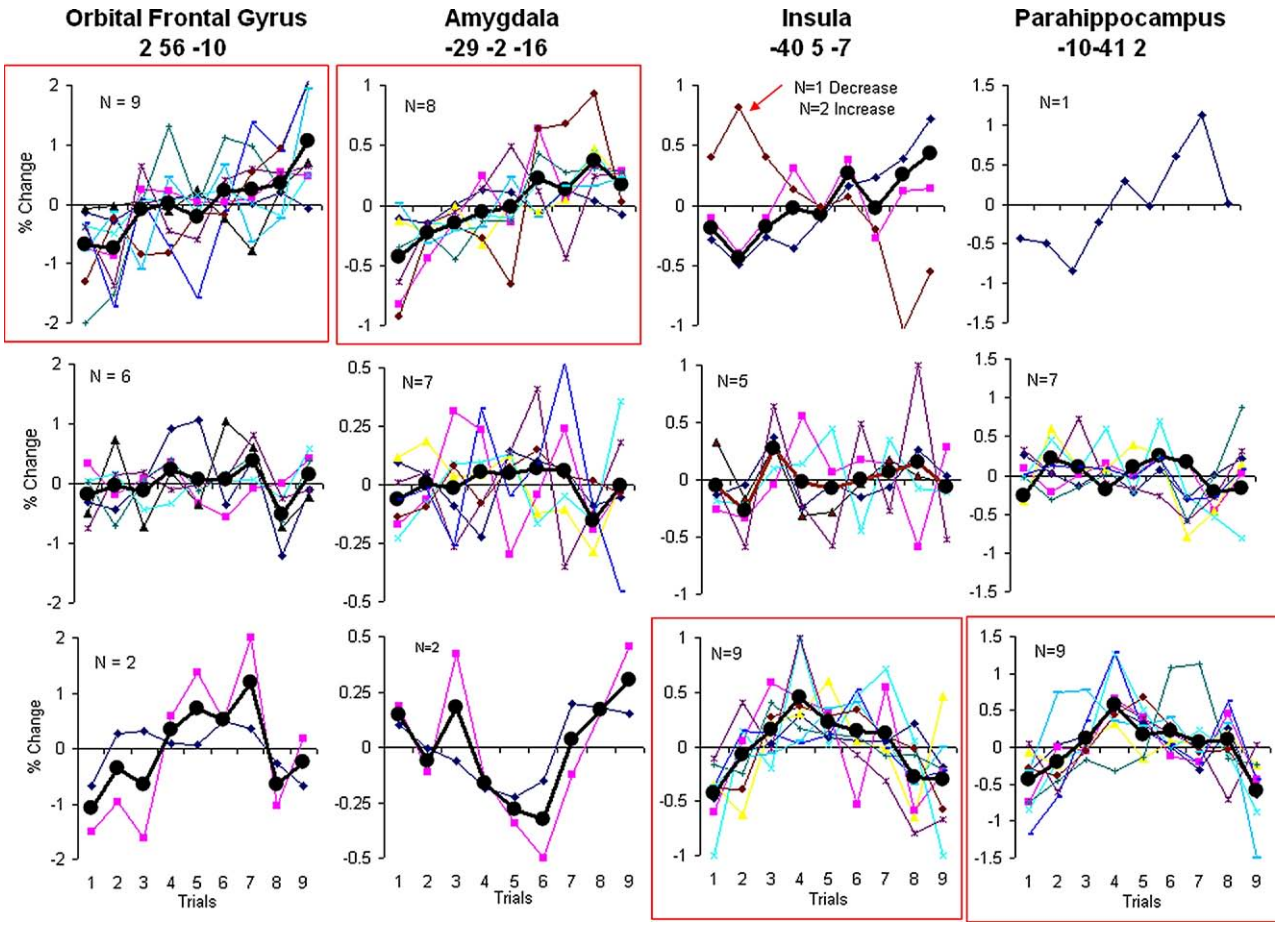

Fig. 2. Individual subject regional changes in activation to consecutive S+ cue presentations. Plots show changes in the percentage of global mean intensity beginning with the first trial reinforced trial (which was either trial 1 or 2) and ending with the ninth reinforced trial. For each region, the first row of plots highlights linear increases in activation, the second row undifferentiated changes and the third row curvilinear (U and inverted-U shaped) changes in activation. Within each plot filled circles represent mean levels of activation. Plots boxed in red highlight the characteristic group change in activation appearing in Fig. 1. The number of subjects appearing in each plot is also listed.

dala regions, a phasic response profile was observed in the insula, as well as the hippocampus/parahippocampus. The profile was characterized by steady increases in activation across reinforcement trials one to four that subsided over reinforcement trials five to nine, suggesting involvement is limited to early acquisition.

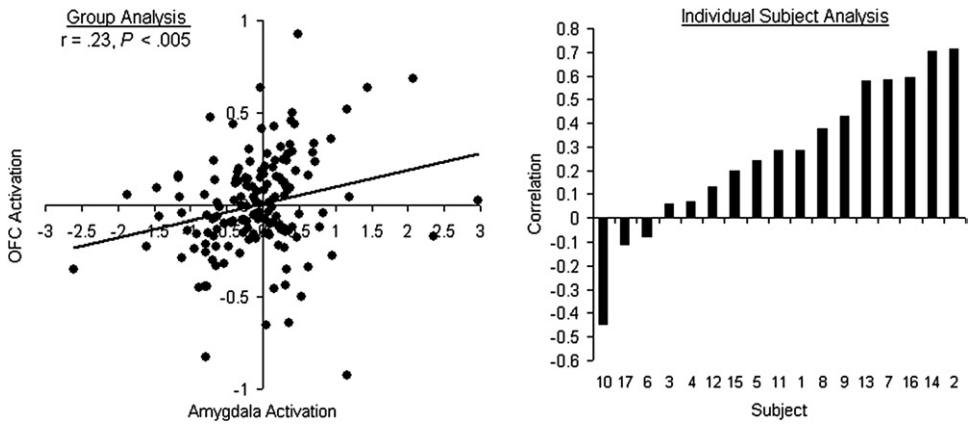

Fig. 3. Relationship between orbitofrontal and amygdala activation. Results of a regression analysis (left plot) performed between S+ cue related activation in the left orbitofrontal region and the amygdala revealed a significant positive correlation. The right plot presents individual subject correlations rank ordered by magnitude. Results show considerable between subject variability in the strength of the OFC-amygdala relationship.

The present findings also highlight the need for additional investigations on the relationship between frontal and limbic responses and structural and functional characteristics of contingency. With regard to the changes observed in frontal regions, one might expect that if activation reflected regulation of the target response, once responding was acquired and reinforced (Trial 1) there would be a subsequent decline in activation with practice or activation would remain stable. One approach to testing the idea of frontal regulation of overt responding would be to employ a positive reinforcement contingency that differentially reinforced non-responding with money (i.e., differential reinforcement of other behavior (DRO)). Findings showing escalating activation in the absence of overt responding might argue against response regulation. The observed escalation in activation might have reflected increases in the local rate/density of reinforcement, which accompanies increased contingency control. Whether systematic increases and decreases in activation occur with changes in reinforcer density/rate remains to be examined. Cumulative monetary earnings across trials may also have facilitated an escalation in activation independently of the programmed contingency. But this view is problematic on the grounds that cumulative earnings across the session were far greater. If escalation was a function of "runs" of monetary gains, the effects verbal feedback, which arguably lacks the same motivational properties as money, could be examined. Another strategy could be to employ a negative reinforcement contingency in which avoidance responding results in no monetary loss. Under avoidance, a reinforcement contingency and an overt response would be present but accurate responding would produce no monetary gains across trials.

A secondary goal of the present investigation was to assess the correspondence between regional changes in activation identified in group results with individual subject findings. We noted it is rather uncommon within human neuroimaging research to determine the extent of correspondence, but such assessments may be illuminating. Our analyses of individual subject changes in activation in the orbitofrontal gyrus highlighted that approximately 50% ($n=8$) of subjects exhibited increases in activation, while six subjects showed an undifferentiated (flat) pattern and two subjects showed an inverted U shaped pattern of change. A similar level of variability was observed in the amygdala, insula and parahippocampus. There were also considerable between-subject differences in the strength of the OFC-amygdala relation which ranged from -0.45 to $+0.75$. While such discrepancies may question what conclusions can be drawn from group results, we believe such disparities highlight a unique opportunity for exploring individual differences in regional sensitivity to contingency as well as improving experimental preparations to better highlight and control the effects of extraneous variables. In this investigation, we have every confidence that the observed level of between-subject variability was not related to our procedures, as response accuracy and reaction times across trials and sessions were highly stable. It will be necessary for future investigations to consider whether some of the between-subject differences observed may, for example, represent gender differences in sensitivity to classical and operant learning processes (e.g., Dalla and Shors, 2009) or represent individual differences associated with learning-to-learn that would be present in some degree in repeated acquisition methodologies.

It seems worthy to note that the present investigation failed to replicate some of our prior findings and those reported in related investigations on contingency control. Relative to our prior investigation, the absence of effects may be attributed to our small sample and fewer trials as well as to different contingencies. In particular, systematic changes were not observed in the anterior cingulate, which has been implicated in the integration of monetary reward with motor responses (Williams et al., 2004) and probabilistic learning (Santesso et al., 2008), or the striatum, which facilitates reward based learning (Haruno et al., 2004; Delgado et al., 2005). One contributing factor may have been that our prior investigation employed a task that involved alternating between a cue correlated with a positive reinforcement contingency and a cue correlated with an ambiguous contingency that neither reinforced nor punished responding or non-responding (resembling extinction). In contrast, the present task involved alternating between two cues correlated with a similar positive reinforcement contingency. The extent to which such differences impact changes in neural activation remain unclear, but presumably responding under similar contingencies in the present investigation may have been less provocative and minimized conflict related activation in the anterior cingulate (Botvinick et al., 2004; Ridderinkhof et al., 2004).

CONCLUSION

In summary, the linear increases in activation observed in superior, medial and orbitofrontal regions as a function of cumulative reinforcement suggest involvement in discriminating contingency and highlights that regional changes continue with subsequent reinforcement even when behavior characteristics (accuracy, reaction time) remain stable. Results also highlighted a positive correlation between changes in OFC activation and amygdala activation that is consistent with the hypothesized working relationship between these regions in behavioral regulation. However, inspection of the correspondence between group changes and individual subject changes in activation revealed that approximately half of subjects exhibited changes resembling group changes and the strength of the OFC-amygdala relationship varied markedly between subjects. Further research is needed to determine whether such disparities highlight individual differences in regional sensitivity or the effects of extraneous variables.

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