Separate neural systems for behavioral change and for emotional responses to failure during behavioral inhibition

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Abstract

To analyze the involvement of different brain regions in behavioral inhibition and impulsiveness, differences in activation were investigated in fMRI data from a response inhibition task, the stop-signal task, in 1709 participants. First, areas activated more in stop-success than stop-failure included the lateral orbitofrontal cortex extending into the inferior frontal gyrus (ventrolateral prefrontal cortex, BA 47/12), and the dorsolateral prefrontal cortex. Second, the anterior cingulate and anterior insula were activated more on failure trials, specifically in stop-failure vs stop-success. The interaction between brain region and stop-success vs stop-failure activations was significant ($p = 5.6 * 10^{-8}$). The results provide new evidence from this 'big data' investigation consistent with the hypotheses that the lateral orbitofrontal cortex is involved in the stop-related processing that inhibits the action; that the dorsolateral prefrontal cortex is involved in attentional processes that influence task performance; and that the anterior insula and anterior cingulate are involved in emotional processes when failure occurs. The investigation thus emphasizes the role of the human lateral orbitofrontal cortex BA 47/12 in changing behavior, and inhibiting behavior when necessary. A very similar area in BA47/12 is involved in changing behavior when an expected reward is not obtained, and has been shown to have high functional connectivity in depression.

Keywords. Inhibition; impulsive behavior; orbitofrontal cortex; cingulate cortex; insula; depression

Introduction

Analyzing brain function in the stop-signal task (SST) is of great interest, for this task is related to behavioral inhibition and impulsiveness, and its performance is impaired in attention-deficit hyperactivity disorder (ADHD) (Aron, et al., 2014). The task has Go trials and Stop trials. During Go trials participants are presented with an arrow pointing either to the left or to the right, and are instructed to make a button response with their fingers corresponding to the direction of the arrow. In the unpredictable Stop trials (17%; 80 trials), the arrows pointing left or right are followed (on average 300 ms later) by an arrow pointing upwards, which instructs participants to inhibit their motor responses (Nymberg, et al., 2013). More details are provided in the Methods. The task design allows measurement of brain activation in relation to response inhibition and its failure. Not only is behavioral inhibition important in its own right and in relation to ADHD, but in addition this process is related to impulsiveness. Further, it is important in terms of understanding the underlying brain mechanisms to know whether the areas involved in behavioral inhibition are similar to or overlap with the areas of the lateral orbitofrontal cortex area involved in reversing behavior to non-reward (Grabenhorst and Rolls, 2011; Rolls, 2014; Rolls and Grabenhorst, 2008; Thorpe, et al., 1983), which have been thereby implicated in depression (Rolls, 2016c; Rolls, 2017).

The overall aim of the investigation described here is to analyze the activations that are measured with functional magnetic resonance imaging (fMRI) in the stop-signal task. The particular aims were as follows. First, previous investigations have highlighted the importance of the inferior frontal gyrus, based on the effects of brain damage (Aron, et al., 2014) and fMRI (Aron, et al., 2014; Boehler, et al., 2010; Cai, et al., 2014; Duann, et al., 2009; Nymberg, et al., 2013; Xue, et al., 2008; Zhang and Li, 2012). However, the inferior frontal gyrus may refer to a number of brain systems that may perform different functions. In particular, the lateral orbitofrontal cortex Brodmann area 47/12 extends in humans round the inferior convexity where it adjoins posteriorly on the lateral surface areas BA 45, which is part of Broca's area on the left; and more anteriorly lateral area 10 (Öngür, et al., 2003; Öngür and Price, 2000; Rolls, et al., 2015). A first aim of this investigation was therefore to identify the focus of the activation in the stop-signal task to clarify whether the focus was in the lateral orbitofrontal, areas in the inferior frontal gyrus, or whether the activation included both. We investigated this is a large group of 1709 individuals in order to obtain robust results and localization. The second particular aim was to investigate whether other areas that we and others found to be activated in the same task in brain regions connected to the lateral orbitofrontal cortex / inferior frontal gyrus were activated in the same way, or differently which would imply different contributions to the task. The other areas included the anterior cingulate cortex, the insula (Cai, et al., 2014), and the dorsolateral prefrontal cortex. We investigated this by contrasting the activations on stop-success trials compared to stop-failure trials. We reasoned that brain regions with larger activations on stop-success trials than stop-failure trials might be involved in the computations involved in stopping the task. We reasoned that brain regions with larger activations on stop-failure trials than stop-success trials might be involved in the emotional response to failure that would be expected to be more evident on stop-failure trials. These particular aims make this a novel investigation.

The data we analyzed were from 1709 participants in the IMAGEN database (Nymberg, et al., 2013). The dataset is by far the largest one to include the SST, and should help to provide

robust and well-localized evidence on the neural processes involved in different aspects of the stop-signal task. This particular dataset has the interesting and useful property that all the participants were of a similar age, 14 years old, enabling processes at this important stage of development with respect to behavioral control and impulsiveness, important developments in adolescence (Nymberg, et al., 2013), to be investigated, and ensuring a homogeneous population with respect to age. Individuals of this age were suitable for investigation of inhibition, for the stop-signal task was performed in a similar way to that described in older individuals (Cai, et al., 2014). A further advantage of this dataset is that all participants performed the same stop-signal task with similar imaging parameters.

A new key finding of this investigation is that a cortical area involved in the success of behavioral inhibition on the stop-signal task is the lateral orbitofrontal cortex BA47/12. Another new key finding is that this function is dissociable from the functioning of the insula and anterior cingulate cortex in the stop-signal task, which are activated more on failure trials.

The architectonic areas of the human orbitofrontal cortex have been described by Price and colleagues (Öngür, et al., 2003), and their analysis shows that the lateral orbitofrontal cortex Brodmann area 47/12 continues round the inferior convexity to include the ventral part of the inferior temporal gyrus where it adjoins BA 45 posteriorly and lateral area 10 anteriorly. This area has been variously referred to as the ventrolateral prefrontal cortex (VLPFC), inferior frontal gyrus, and lateral orbitofrontal cortex. The focus of the activations in stop-success – stop-failure described in this paper was in the lateral orbitofrontal cortex BA 47/12 (Öngür, et al., 2003), and when other terms are used in this paper this is because they have been used in the literature.

Methods

Task / Experimental Design

The stop-signal task (SST) is an event-related task designed to study neural responses involved in successful and unsuccessful inhibitory control, with full details provided in (Nymberg, et al., 2013), and an illustrative diagram in Fig. 1. The task has Go trials (83%; 400 trials) and Stop trials (17%; 80 trials), with between three and seven go trials between two stop trials. It required participants to respond to visual go stimuli (arrows pointing left or right) and to withhold their motor response when the go stimulus was followed unpredictably by a stop signal (an arrow pointing upwards). A tracking algorithm changed the time interval (on average 300 ms with initial delay = 250 ms), that is, the stop signal delay (SSD) , between the Go signal and Stop signal onsets on Stop trials adaptively to produce 50% successful and 50% unsuccessful response inhibition trials. The inter-trial interval was 1,800 ms. The stop signal reaction time (SSRT) was calculated by subtracting the mean stop signal delay (the average time between go and stop signal, at which the subject managed to inhibit to 50% of stop trials) from the mean reaction time to go trials.

Subjects

Data were acquired from 1980 14-year-old adolescents from the IMAGEN initiative across eight IMAGEN assessment sites (Nymberg, et al., 2013), who had participated in the SST task. A total of 1709 participants from these passed quality controls for neuroimaging and behavioral

tests and were included into further analysis (Nymberg, et al., 2013). (The dataset included 882 females, 827 males; 1493 were right-handed, 192 left-handed, and 24 had missing handedness records; the go reaction time had a mean of 470 ms, std 81 ms; the stop success reaction time had a mean of 234 ms, std 91 ms.) This dataset was used because it was homogeneous for age so that possible age differences did not need to be factored out; because impulsiveness and behavioral inhibition are key factors in adolescent development, and understanding how these processes operate at this developmental stage has potential clinical implications (Nymberg, et al., 2013); and because the large size of the cohort is an advantage in neuroimaging analyses to obtain robust results and accurate localization, and to enable whole-brain analyses without selection of only some brain regions using a priori hypotheses. In these respects, the present study is an advance beyond previous studies on behavioral inhibition investigated with the stop-signal and similar tasks. The individuals understood and performed the task well in the scanner, as shown by the behavioral measures (Nymberg, et al., 2013).

Functional Magnetic Resonance Imaging Data Acquisition and Preprocessing

Functional magnetic resonance imaging (fMRI) data were acquired for the SST task with 3T MRI scanners. All data acquisition, preprocessing, and quality controls were performed by the IMAGEN initiative, with the detailed procedures and parameters provided in detail elsewhere (Nymberg, et al., 2013; Whelan, et al., 2012). Briefly, functional MRI BOLD images were acquired with a gradient-echo, echo-planar imaging sequence. For the stop-signal task, 444 volumes were acquired for each subject, while each volume consisted of 40 slices aligned to the anterior commission/posterior commission line (2.4-mm slice thickness, 1-mm gap). The echo time was optimized (echo time = 30 ms, repetition time = 2200 ms) to provide reliable imaging of subcortical areas. Image processing and analysis were performed using SPM 8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Time series data were corrected for slice timing, then for movement, non-linearly warped onto MNI space using a custom EPI template, and Gaussian-smoothed at 5-mm full-width half maximum. Estimated movement (three translations, three rotations, three translations shifted one volume acquisition before and three translations shifted one volume acquisition later) parameters were added as nuisance variables. Each fMRI time series underwent automatic spike detection and any artifactual time points were regressed out of each subject's data. Activation maps and contrast maps were computed using a general linear model with an autoregressive noise model. Based on behavioral records, each participant's design matrix included regressors for stop success trials, stop failure trials, trials on which the go response was too late, trials on which the go response was wrong (if any) and the nuisance variables. The regressors modeling the experimental conditions were convolved using SPM's default hemodynamic response function. A one-sample *t* test was conducted, testing activity on stop success trials (and separately on stop fail trials), removing variance associated with the other regressors in the design matrix. Beta values of contrast maps were used for further analysis, and all the following analysis was performed using Matlab.

All the templates are in MNI space and voxel activations are presented in MNI coordinates. Results were analyzed for contrast maps that included stop-success – stop-failure as this potentially provides evidence about the brain systems that implement behavioral inhibition; and also stop-failure – stop-success as this potentially provides evidence about brain systems

activated by failure in the task.

The IMAGEN data come from multiple data collection sites. To test whether there was any significant variation between sites, we performed a two factor ANOVA with one factor the sites and the other factor the four brain regions considered here in stop-success – stop failure. No significant intersite variation was found (all p values were in the range 0.81 – 0.95).

Results

First, in order to identify brain regions that are likely to be important in successful performance of the SST, we present the results for the contrast of stop-success – stop-failure. Then we analyze the contrast stop-failure – stop success, because this may reveal areas that may be more related to other processes, such as emotional responses to failure. Then we present results for other contrasts. These analyses are based on data from 1709 participants. We emphasize results for areas implicated in behavioral change and emotion by lesion and much other evidence, and this includes brain regions such as the orbitofrontal cortex and inferior frontal gyrus, anterior cingulate cortex, and insula (Aron, et al., 2014; Rolls, 2014; Rolls, 2015a; Rolls, 2016a; Rolls, 2016b).

Contrast of stop-success – stop-failure

The results for the contrast stop-success – stop-failure are illustrated in Fig. 2a, and 2b with further details in Table 1, with three regions described next. The first region is the ventrolateral prefrontal cortex, with peak at [-42 50 -2] (t=5.1, p=3.58e-7, significant under FDR correction for the whole brain), and with corresponding effects on the right [42 52 -4] (t=2.8, p=0.0052). This region includes the lateral orbitofrontal cortex BA 47/12 which includes part of the inferior frontal gyrus (Öngür, et al., 2003; Rolls, et al., 2015).

The second region is the dorsolateral prefrontal cortex, with peak at [38 44 38] (t=5.0, p=6.02e-7, significant under FDR correction for the whole brain).

Another interesting region is the pars opercularis of the right inferior frontal gyrus, with a peak at [50,16,34] (t=3.0, p=0.0028), which is probably BA 45 or 44 (Öngür, et al., 2003; Rolls, et al., 2015).

These regions are of particular interest for the analysis of this task because the lateral orbitofrontal cortex is involved in changing behavior when non-reward or punishment is received (Kringelbach and Rolls, 2003; Rolls, 2014; Rolls, 2016c; Rolls and Grabenhorst, 2008); and lesions of the (right) inferior frontal gyrus that are close to the contrast peaks just described impair the performance of the SST (Aron, et al., 2014). (They described the region as BA 44 inferior frontal gyrus, opercular part in the AAL atlas (Tzourio-Mazoyer, et al., 2002).) In addition to these contrasts of especial interest, effects were also found as shown in Table 1 in the ventral striatum (which receives inputs from the orbitofrontal cortex and other parts of the prefrontal cortex (Haber and Knutson, 2010)), premotor cortex (which may reflect the change of movement), inferior temporal gyrus (and related visual areas), and parietal cortex area 7 (both of which receive back projections from the prefrontal cortex (Pandya, et al., 2015; Rolls, 2016a)).

Contrast of stop-failure – stop-success

In the contrast stop-failure – stop-success, the anterior insular cortex showed effects ([-46

8 -2] t=8.3, p=2.22e-16; [46 12 2] t=5.3, p=1.23e-7), as did the supracallosal anterior cingulate cortex ([-2 18 38] t=9.2, p=6.06e-20; [4 30 26] t=8.5, p=2.80e-17) (see Fig. 2c, 2d and Table 2). It is of interest that these activations were largest on the left of the brain. The effects in both these areas may be related to the emotional responses to the failure, for this anterior insular region is implicated in autonomic effects (Critchley and Harrison, 2013; Rolls, 2016b), and this part of the anterior cingulate cortex is implicated in the representation of aversive / unpleasant events (Grabenhorst and Rolls, 2011; Rolls, 2014; Rolls and Grabenhorst, 2008).

In summary, stop-failure activates the anterior insula more than stop-success, especially the ventral anterior insula (see Fig. 2d); and further, both types of stop trials activate the anterior insula more than Go trials (two sample t-test between stop-success and Go, with stop-success > Go, t = 28.98, p = 2.54e-162; two sample t-test between stop-failure and Go, with stop-failure > Go, t = 30.56, p = 3.45e-178). Activation on Go trials was found in the posterior insula. Also shown in Table 2 are effects in movement-related cortical areas such as the pre- and post-central gyrus, which are likely given the functions of these regions to be related to the motor responses which are different on stop-failure trials (on which a response is completed) than on stop-success trials (on which a movement is not completed).

Other contrasts

Fig. 3a shows the activation produced in the stop-success condition. This shows that the area activated extends from the orbitofrontal cortex though the lateral orbitofrontal cortex Brodmann area 47/12 (Öngür, et al., 2003) to the inferior frontal gyrus, and up to the dorsolateral prefrontal cortex.

Fig. 3b shows that on the Go-success trials, the ventromedial prefrontal cortex, including the medial orbitofrontal cortex BA13, is activated. This is consistent with its role in representing many different rewards (Grabenhorst and Rolls, 2011; Rolls, 2014), with the reward in this case the simple completion of a Go trial which corresponds to correct performance of the typical trial type in this task. It is noted that in the Go-Success condition, the activation was much lower than on stop-success in the lateral orbitofrontal cortex 47/12 / inferior frontal gyrus region (t = -22.54, p = 2.09e-97), than in the dorsolateral prefrontal cortex (t = -39.20, p = 1.06e-237), than in the anterior cingulate cortex (t = -49.27, p < 4.94 e-324 , and than in the insula (t = -28.98, p = 2.54e-162). This indicates that these four regions have activations that are related to the stop trials, rather than the Go trials.

Dissociation between brain regions involved in stop-success and stop-failure

To investigate whether the activations in the areas of interest are different on stop success – stop failure trials (which may reflect engagement of brain regions necessary to change the behavior) from the activations on stop-failure - stop-success trials, we performed a two way analysis to test for significant interaction between these contrasts and brain regions.

Fig. 4 illustrates the dissociation between the greater activations in stop-success in the Lateral Orbitofrontal Cortex (OFC) and dorsolateral prefrontal cortex (DLPFC), versus the greater activations in stop-failure in the anterior insula and anterior cingulate cortex, with the dissociation confirmed by a significant interaction effect in a two-factor ANOVA involving the 4 brain regions × the two contrasts $F[3,13664] = 12.21$, with p-value = $5.61 * 10^{-8}$.

Comparing brain regions of particular interest, the interaction statistic for Lateral

Orbitofrontal cortex and Insula vs contrast is F[1,6832] = 13.04, with p-value = 3.08 * 10^{-4}. This shows that the Lateral Orbitofrontal cortex and the insula are activated differently as a function of these two contrasts. The interaction statistic for Lateral Orbitofrontal Cortex and Anterior Cingulate Cortex vs contrast is F[1, 6832]= 18.53, with p-value = 1.69 * 10^{-5}. This shows that the Lateral Orbitofrontal Cortex and the anterior cingulate cortex are activated differently as a function of these two contrasts.

Discussion

Some of the new findings and advances made in this paper, made possible by the large sample size, whole-brain analysis with no a priori regions of interest, and the identical stop-signal task (SST) performed by all 1709 participants, include the following which are discussed below. These attributes of this investigation enable it to go beyond previous studies which had fewer subjects and/or used a priori regions and/or which combined results from several tasks (Aron, et al., 2014; Boehler, et al., 2010; Cai, et al., 2014; Duann, et al., 2009; Xue, et al., 2008; Zhang and Li, 2012). First, the peak of the activation in successful trials of the stop-signal task in the inferior frontal gyrus / inferior convexity prefrontal cortex (Fig. 2a) is in an area that is part of area 47/12, a lateral orbitofrontal cortex region (Öngür, et al., 2003). This is more clearly shown to be lateral orbitofrontal cortex area 47/12 than in some earlier studies (Aron, et al., 2014; Boehler, et al., 2010; Cai, et al., 2014; Duann, et al., 2009; Xue, et al., 2008; Zhang and Li, 2012). This is important, for it helps to identify this system as a lateral orbitofrontal cortex region activated in other types of task in which behavior must change, namely tasks in which a non-reward signals that behavior should change, and in which punishers / aversive stimuli are received (Grabenhorst and Rolls, 2011; Rolls, 2014; Rolls, 2016c). Second, a dissociation of brain areas activated in the SST was found, with the finding for the first time that the lateral orbitofrontal cortex and dorsolateral prefrontal cortex are activated relatively more on successful than on failure trials, whereas the insula and anterior cingulate cortex are relatively more activated on failure than on reward trials. This again is important, for this finding provides evidence on which brain systems are especially important in performing the stop-signal task correctly, and on other brain areas that respond more with failure. The new findings help to provide a framework for understanding the functions of these four areas in the SST and in behavioral inhibition, and are discussed next.

First, we consider areas activated in the contrast stop-success – stop-failure. Areas identified in this contrast are candidates for contributing to the successful implementation of stopping the action when the Stop signal is received. One of these areas is the lateral orbitofrontal cortex area BA 47/12 which extends into the inferior frontal gyrus (Fig. 2a and Table 2) as defined cytoarchitectonically in humans (Öngür, et al., 2003), and thus includes more than the opercular part of the inferior frontal gyrus that is often emphasized as being involved in the stop-signal response inhibition task (Aron, et al., 2014; Rae, et al., 2015). This region is of particular interest for the analysis of this task because the lateral part of the orbitofrontal cortex is activated by many aversive stimuli, and when behaviour must be changed when reward is not received (Grabenhorst and Rolls, 2011; Kringelbach and Rolls, 2003; O'Doherty, et al., 2001; Rolls, 2014; Rolls and Grabenhorst, 2008), and lesions of the (right) inferior frontal gyrus that are close to the contrast peaks in this region impair the performance of the SST (Aron, et al., 2014). (They described the region as inferior frontal gyrus, opercular

part in the AAL atlas (Rolls, et al., 2015; Tzourio-Mazoyer, et al., 2002).)

A hypothesis that is consistent with these findings and with the literature (Grabenhorst and Rolls, 2011; Kringelbach and Rolls, 2003; Rolls, 2014; Rolls, 2016c; Rolls and Grabenhorst, 2008) is that this lateral orbitofrontal cortex / inferior frontal gyrus BA47/12 region is involved in the stop-related processing that inhibits the action. Indeed, the activation of the lateral orbitofrontal cortex / ventrolateral prefrontal cortex in stop-success – stop-failure (Fig. 2a) is very similar indeed to that in the lateral orbitofrontal cortex on reversal trials in visual discrimination reversal, when non-reward is obtained and behavior must change (Kringelbach and Rolls, 2003) (with a similar lateral orbitofrontal cortex area activated in macaques (Chau, et al., 2015)). At the neuronal level, error-related neurons that respond when behavior must be changed due to non-reward or punishment are found in the orbitofrontal cortex (Thorpe, et al., 1983), and are part of the mechanism for the change of behavior, in that reversal learning is impaired by damage to this region (Grabenhorst and Rolls, 2011; Hornak, et al., 2004; Rolls, 2014; Rolls and Grabenhorst, 2008; Rolls, et al., 1994). The functional connectivity of this region with the temporal cortical visual areas (Cheng, et al., 2016) provides interesting evidence on the region of the ventrolateral prefrontal cortex that receives visual inputs, consistent with anatomical evidence (Pandya, et al., 2015; Petrides, et al., 2012; Yeterian, et al., 2012), and indeed is likely to be the route via which the visual stop signal reaches the ventrolateral prefrontal cortex BA 47/12. Possible routes for this lateral orbitofrontal cortex system to influence action include (1) via the opercular and nearby parts of the inferior frontal gyrus (area 44) which in turn has connections with the preSMA (the pre-supplementary motor area, referred to in this paper as medial prefrontal cortex / area 8), both of which are implicated in this response inhibition task (Rae, et al., 2015); (2) via subcortical structures such as the striatum / basal ganglia (caudate, putamen, ventral striatum, globus pallidus) which are activated (Tables 1 and 2) and implicated (Rae, et al., 2015) in this task; and (3) via connections to the anterior cingulate cortex (Grabenhorst and Rolls, 2011; Rolls, 2014). It is notable that aspects of social cognition dependent on this inferior frontal gyrus region are developing rapidly during the stage of adolescence investigated here (Kilford, et al., 2016).

A second of these areas activated by the contrast stop-success – stop-failure is the dorsolateral prefrontal cortex (Fig. 2b). A hypothesis that is consistent with the literature (Fuster, 2001; Fuster, 2008; Goldman-Rakic, 1996; Rolls, 2008; Rolls, 2016a) is that this region is involved in short-term memory and attention, so that greater activation of this region on stop-success – stop-failure may reflect the influence of good attention on the performance of the SST. In more detail, the dorsolateral prefrontal cortex (DLPFC, BA9/10/46) and ventrolateral prefrontal cortex (BA44/45) regions are implicated in working memory (Goldstein, et al., 2011), with VLPFC / BA44/45 maintaining information and DLPFC monitoring and manipulating information (Petrides, 1994; Petrides, 1995). The monitoring function of the DLPFC is reported to serve behavior control (Cieslik, et al., 2013), such as when we need to adapt our behavior to a changing environment, override habitual responses, or shift between different tasks (Hoshi, 2006; Mansouri, et al., 2009; Miller and Cohen, 2001; Passingham and Sakai, 2004), which supports the hypothesis that the DLPFC plays an important role in the SST. Further, the right DLPFC is especially implicated in working memory (Goldstein, et al., 2011; Kane and Engle, 2002), monitoring (Shallice, 2004; Vogt, et al., 2007), and resolution of conflict during motor response execution (Aron, et al., 2003; Aron, et al., 2004; Nee, et al., 2007), all of which are

consistent with research linking hemispheric lateralization with type of task (for example, spatial with right, verbal with left) (Petrides, 1994; Petrides, 1995). This evidence is consistent with the findings of the present analysis with larger effects in the right dorsolateral prefrontal cortex, for the SST involves processing of spatial information provided by arrows on the screen that direct responses made by the hand.

Second, we consider areas that were activated in the strength order stop-failure (SF) > stop-success (SS). More precisely, we performed a two-sample t-test between the pair of conditions (SF, SS) for the average activation strength in the regions of Anterior Insula (AI) and Anterior Cingulate cortex (ACC) separately. For AI, SF > SS ($t=2.7$, $p = 0.0063$). For ACC, SF > SS ($t = 3.7$, $p = 2.1 * 10^{-4}$). We also performed the interaction analysis illustrated in Fig. 4, which strongly supports the dissociation (p-value = $5.61 * 10^{-8}$). These areas of especial interest in this task were the anterior cingulate region and the anterior insula. The fact that these areas had activations in the order just described is consistent with the hypothesis that they are involved in the emotional processes that occur when failure occurs, and in the emotional processes that occur when an action must be aborted, with the smallest activation on trials on which the action proceeds to completion. On the failure trials, an error in an action has occurred, and this may produce an emotional response. This hypothesis is consistent with the evidence that the part of the anterior cingulate cortex just dorsal and posterior to the genu of the corpus callosum is the cingulate region in which many aversive and unpleasant events are represented, including unpleasant tastes, odors and flavors, painful stimuli, and changing behavior when an expected visual stimulus is not obtained in the reversal of a visual discrimination task (de Araujo, et al., 2003; Grabenhorst and Rolls, 2011; Kringelbach and Rolls, 2003; Rolls, 2014; Rolls, et al., 2003a; Rolls, et al., 2003b). The anterior and midcingulate cortex are implicated in action-outcome learning, that is learning whether actions are associated with reward or punishment (Grabenhorst and Rolls, 2011; Rolls, 2014; Rushworth, et al., 2011), and contains neurons that respond when errors in actions occur and rewards are reduced (Niki and Watanabe, 1979; Shima and Tanji, 1998). The pregenual cingulate cortex in contrast was not activated in the SST, consistent with the evidence that for comparison its activations are related to rewarding, subjective pleasant stimuli (Grabenhorst and Rolls, 2011; Rolls, 2014; Rolls and Grabenhorst, 2008), and not to correcting errors such as having to change behavior, in for example reversal, or to aversive stimuli (Grabenhorst and Rolls, 2011; Kringelbach and Rolls, 2003; Rolls, 2014). Parts of the anterior insula located anterior and ventral to the insular taste cortex are part of the visceral cortex involved in autonomic responses (Critchley, 2005; Critchley and Harrison, 2013; Rolls, 2014; Rolls, 2015b; Rolls, 2016b; Simmons, et al., 2013), which will be engaged by emotional states such as failure in a task. This anterior cingulate – anterior insula system has also been termed a 'saliency' network (Menon and Uddin, 2010), and salient stimuli may often be aversive, and are likely to produce autonomic responses (Rolls, 2016b). Indeed, we note that the hypothesis described here is different from (and more parsimonious than) the hypothesis of Menon et al. (Cai, et al., 2014; Menon and Uddin, 2010), that the anterior insula is involved in "salience detection". (It is noted that activations to "salience detection" might alternatively be cast as activations to rewarding, punishing, and novel stimuli all of which might elicit behavioral and autonomic output (Rolls, 2014; Rolls, 2016b).)

A highlight of this study is that the large number of participants enabled voxel-level

analysis of the data in a purely data driven way, with no a priori hypotheses on particular brain regions that could limit the results. This makes the results very robust, as shown by the significance values obtained.

In the context of previous research, differences of the present study from previous investigations of the stop-signal task enable it to go beyond previous studies which had in general far fewer participants and/or used a priori regions and/or which combined results from several tasks (Aron, et al., 2014; Boehler, et al., 2010; Cai, et al., 2014; Duann, et al., 2009; Xue, et al., 2008; Zhang and Li, 2012). Further, differences from a previous investigation of inhibition (Cai, et al., 2014) are that in the present investigation meta-analysis was not needed to identify a priori regions of interest for the analysis as there is a single set of 1709 participants in the present study so enabling an unbiased brain-wide voxel-level study, allowing very much more statistical power and potentially significance of the findings; that our analysis is entirely based on task-related data with 1709 participants; and in that we focused on analysis in a single task, rather than including data from a number of different tasks. The present investigation differs from an earlier investigation of an overlapping dataset (Whelan, et al., 2012) by focusing on how different brain systems contribute to different processes involved in response inhibition, and its failure. Another strength of the present investigation is that use of the IMAGEN database allowed the data to be collected from a large cohort of individuals all of a similar adolescent age, so that age-related factors did not need to be regressed out of the analysis.

A limitation of this investigation is that it would have been of interest to include a different type of task requiring behavioral change, to allow direct comparison. The stop-signal task required a response to be changed: stopped. A reward reversal task requires the association of a stimulus with reward to be changed, and this will change whether that stimulus is selected in future. This type of learning is stimulus-reward association and reversal, and requires a stimulus-stimulus association to be changed, where the second stimulus is the reward outcome (Rolls, 2014; Rolls and Deco, 2016). Neurons in the primate orbitofrontal cortex respond to this non-reward signal, which is a mismatch between what is expected and what is obtained as the outcome; and the reward expectation neurons reverse the stimulus to which they respond (Thorpe, et al., 1983). The crucial part of the orbitofrontal cortex for this reward reversal as shown by activation studies is the lateral orbitofrontal cortex (Chau, et al., 2015; Kringelbach and Rolls, 2003; Rolls, 2014; Rolls, 2016c). This concept of a non-reward and punishment system involving the lateral orbitofrontal cortex (Rolls, 2016a) has been developed into a theory of depression in which the non-reward attractor-related firing of the orbitofrontal cortex neurons is over-responsive in depression (Rolls, 2016c; Rolls, 2017). The interesting point here is whether there is a similar system in the lateral orbitofrontal cortex for non-reward detection which indicates that a reward association should be changed, and for the detection of a stop or error signal informing the participant that a response should be changed. Although it is a limitation that this could not be addressed in the present analysis by a direct comparison in the same participants, the present study does make the important new point that the stop-signal task and reward reversal are tasks that require similar computations of an error, which in turn leads to behavioral change, and both involved lateral orbitofrontal cortex areas. It will be interesting in future work to examine this relationship further, by including both tasks in the same study, or be recording single neuron activity in the orbitofrontal cortex in both types of task.

The findings are of interest in that performance in the SST provides evidence about behavioral inhibition and impulsiveness, and the performance of the task is impaired in attention-deficit hyperactivity disorder (Aron, et al., 2014). The finding described here that the lateral orbitofrontal cortex is a region implicated in behavioral change of the response inhibition type is important for this helps to focus attention on this brain region as a key region involved in a number of behavioral change, non-reward, and reward reversal functions that are fundamental to social and emotional behavior, and in impulsive behavior (Aron, et al., 2014; Rolls, 2014; Rolls, 2016c). An important finding of the present study for the understanding of the mechanisms of behavioral change is that the region most implicated in this is a ventrolateral part of the prefrontal cortex which is lateral orbitofrontal cortex area BA47/12 (Öngür, et al., 2003; Öngür and Price, 2000). This is relevant for example to the brain mechanisms that are different in patients with depression, who have increased functional connectivity of parts of BA47/12 with the precuneus, angular gyrus, and inferior temporal cortex (Cheng, et al., 2016), consistent with the hypothesis of overactive networks in depression in this region which is implicated in non-reward and behavioral change (Rolls, 2016c).

Table 1. Contrasts for stop-success – stop-failure

ROI	Full name of ROI	Cluster center coordinates	Highest t-score (p-value)
1	Ventrolateral Prefrontal cortex / Lateral Orbitofrontal Cortex	(-42,50,-2)	5.1 (3.58e-7)
2	Dorsolateral Prefrontal cortex	(38,44,38)	5.0 (6.02e-7)
3	Ventral Striatum	(22,12,-8)	8.0 (1.78e-15)
4	Premotor Cortex	(30,-8,64)	5.0 (6.02e-7)
5	Inferior Temporal Gyrus	(54,-58,-8)	3.9 (9.80e-5)
6	Parietal	(-48,-58,50)	4.6 (4.38e-6)
7	Brodmann Area 19	(28,-80,-14)	4.3 (1.76e-5)

Table 2. Contrasts for stop-failure – stop-success

ROI	Full name of ROI	Cluster center coordinates	Highest t-score (p-value)
1	Anterior Cingulate Cortex	(-2,18,36)	9.2 (6.06e-20)
2	Insula	(-46,8, -2)	8.3 (2.22e-16)
3	Brodmann Area 4 (primary somatomotor area)	(-44, -2,8)	6.9 (6.18e-12)
4	Postcentral gyrus	(-58, -18,46)	7.2 (7.36e-13)
5	Postcentral gyrus	(-60, -18, 22)	7.5 (8.08e-14)
6	Posterior Thalamus	(-2, -22, 6)	8.1 (6.66e-16)

Figure Legends

Fig. 1. The stop-signal task. (Fig1.eps)

Fig. 2. Contrast maps for stop-success – stop-failure; and for stop-failure – stop-success. All contrast maps were thresholded at $p < 0.05$ with Bonferroni correction across the whole brain, corresponding to t=4.75. The calibration bar in this and subsequent figures shows the t value for the contrast.
(a) The contrast stop-success – stop-failure for ventrolateral prefrontal cortex (VLPFC) including the Lateral Orbitofrontal Cortex, with peak at [-42 50 -2] (t=5.1, p=3.58e-7, significance reported unless otherwise stated using FDR correction for the whole brain). There were corresponding effects on the right [42 52 -4] (t=2.8, p=0.0052).
(b) The contrast stop-success – stop-failure for dorsolateral prefrontal cortex (DLPFC), with peak at [38 44 38] (t=5.0, p=6.02e-7).
(c). The anterior insular cortex in the contrast stop-failure – stop-success showed effects ([-46 8 -2] t=8.3, p=2.22e-16 at crosshairs; [46 12 2] t=5.3, p=1.23e-7).
(d) The supracallosal anterior cingulate cortex in the contrast stop-failure – stop-success showed effects ([-2 18 38] t=9.2, p=6.06e-20 at crosshairs; [4 30 26] t=8.5, p=2.80e-17).
(Fig2.eps)

Fig. 3. Further neuroimaging results.
(a) The activation for stop-success thresholded at p<1e-8, corresponding to t=5.75, to show the regions of the lateral orbitofrontal cortex and dorsolateral prefrontal cortex that were activated.
(b). Contrast of Go trials - stop trials. The whole of the ventromedial prefrontal cortex (VMPFC) was more strongly activated than the lateral orbitofrontal cortex areas.
(Fig3.eps)

Fig. 4. The BOLD signal activations (parameter estimates) (mean over the significant voxels using Bonferroni correction +/- sem) for stop-success (green) and for stop-failure (red) for the four main brain regions, Lateral Orbitofrontal Cortex (Lateral OFC) BA47/12, Dorsolateral Prefrontal Cortex (DLPFC), Insula, and Anterior Cingulate Cortex. (Fig4a.eps)

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