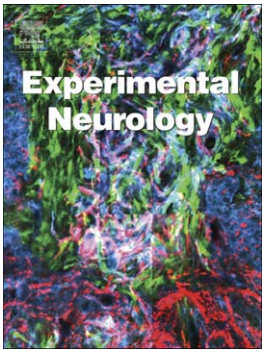

Prefrontal activity in Huntington's Disease reflects cognitive and neuropsychiatric disturbances: The IMAGE-HD study

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Prefrontal activity in Huntington's Disease reflects cognitive and neuropsychiatric disturbances: The IMAGE-HD study

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Abstract

Functional integrity of prefrontal cortico-striatal circuits underlying executive functioning may be compromised by basal ganglia degeneration during Huntington's disease (HD). This study investigated challenged inhibitory attentional control with a shifting response-set (SRS) task while assessing neural response via functional magnetic resonance imaging (fMRI) in 35 healthy controls, 35 matched pre-symptomatic (pre-HD) and 30 symptomatic (symp-HD) participants. A ≥70% performance accuracy threshold allowed confident identification of neural activity associated with SRS performance in a sub-set of 33 healthy controls, 32 pre-HD and 20 symp-HD participants. SRS activated dorsolateral prefrontal and dorsal anterior cingulate cortices, premotor, parietal, and basal ganglia regions and deactivated subgenual anterior cingulate cortex. Symp-HD participants showed greater prefrontal functional responses relative to controls and pre-HD, including larger activations and larger deactivations in response to cognitive challenge, consistent with compensatory neural recruitment. We then investigated associations between prefrontal BOLD responses, SRS performance accuracy and neuropsychiatric disturbance in all participants, including those below SRS performance accuracy threshold. We observed that reduced prefrontal responsivity in symp-HD was associated with reduced accuracy in SRS performance, and with increased neuropsychiatric disturbance within domains including executive dysfunction, pathological impulses, disinhibition, and depression. These findings demonstrate prefrontal response during inhibitory attentional control usefully characterises cognitive and neuropsychiatric status in symp-HD. The functional integrity of compensatory prefrontal responses may provide a useful marker for treatments which aim to sustain cognitive function and delay executive and neuropsychiatric disturbance.

Keywords: Huntington's Disease, fMRI, Set Shifting, DLPFC, Executive Function, Attention

INTRODUCTION

Progressive neurodegeneration in Huntington's Disease (HD) reduces striatal volume in both symptomatic HD (symp-HD) and pre-symptomatic HD (pre-HD) individuals up to 15 years prior to symptom onset (Aylward, et al., 2011, Paulsen, 2011, Paulsen, et al., 2006). Cognitive and neuropsychiatric disturbances also develop (Julien, et al., 2007, Tabrizi, et al., 2012), with cognitive deficits in attention, fluency, executive functioning and memory (Paulsen, et al., 2008, Stout, et al., 2011, Tabrizi, et al., 2009) evident during both pre-HD and symp-HD stages. Neuropsychiatric features include irritability, apathy, and depressive, anxiety and affective spectrum disorders, and are often reported as the most debilitating symptoms (Folstein, et al., 1983, Julien, et al., 2007, Shiwach, 1994). These deficits, which occur independent of motor impairments, can collectively reduce the functional capacity of individuals across a number of domains and thus significantly impact quality of life (Beglinger, et al., 2010).

We investigated functional magnetic resonance imaging (fMRI) responses during a "shifting response set" (SRS) paradigm, and their association with independent measures of cognitive and neuropsychiatric function. SRS tasks require the effective integration of executive functioning and inhibitory control, and rely heavily on the integrity of the prefrontal cortex (Allport, et al., 1994, Jersild, 1927, Lawrence, et al., 1998b). SRS errors within clinical groups, over and above deficits reflecting basic memory and attention, result primarily from perseveration (i.e., difficulty releasing attention from previously relevant) and/or learned irrelevance (i.e., difficulty learning from previously irrelevant) (Owen, et al., 1993). Perseverative and learned irrelevance errors are tied to prefrontal dysfunction. For example, patients with neurosurgical prefrontal lesions demonstrate these errors whereas patients with temporal lobectomy, or resection of amygdala or

hippocampus, do not (Owen, et al., 1991, Robbins, 1996). Prefrontal lesions typically result in disorganised and inappropriate behaviour commonly referred to as "strategy application disorders", highlighting the importance of prefrontal inhibition of irrelevant or inappropriate response strategies which normally underlies appropriate executive and neuropsychiatric function (Goldstein, et al., 1993, Penfield and Evans, 1935, Shallice and Burgess, 1991, Shallice and Burgess, 1993). SRS may be a particularly relevant neuroimaging challenge in HD for two reasons. Firstly, perseverative SRS errors are evident in HD (Lawrence, et al., 1998a, Lawrence, et al., 1996). Secondly, DLPFC activity underlying executive functioning is integrated with striatal activity, a primary region of neurodegeneration in HD (Alexander and Crutcher, 1990, Bonelli and Cummings, 2007, Lawrence, et al., 1998b).

Specifically, we therefore applied fMRI to ascertain, for the first time, how prefrontal SRS responses differ across pre-HD, symp-HD and controls in participants who could *accurately* perform the task. Moreover, we sought to determine how prefrontal activity evoked during SRS related to cognitive and neuropsychiatric function across participants within each group *irrespective of task accuracy*. We hypothesised that accurate SRS performance (≥70% accuracy threshold) would significantly activate DLPFC, dorsal anterior cingulate cortex (ACC) and striatal regions across all groups, with greater responses in pre-HD and symp-HD. Moreover, across *all* symp-HD participants, failure to recruit DLPFC activity would be associated with cognitive (SRS performance accuracy) and neuropsychiatric function.

METHODS

Participants

IMAGE-HD is an ongoing longitudinal study acquiring clinical, neurocognitive, motor, neuropsychiatric and multi-modal neuroimaging measures within symp-HD, pre-HD and matched controls (36 participants per group). In this paper we examined fMRI data during SRS performance, acquired at the first testing time-point. From the total pool of participants, 1 control, 1 pre-HD and 6 symp-HD participants were excluded due to brain pathology unrelated to HD, excessive movement or claustrophobia, leaving a sample of 35 controls, 35 pre-HD and 30 symp-HD participants.

We restricted our first analysis to participants who met an SRS performance accuracy threshold of ≥70%. This was important for our first hypothesis as it allowed confidence that any observed neural response differences (across groups) were not confounded by poor SRS performance. This criterion however reduced our sample to 33 controls, 32 pre-HD and 20 symp-HD participants. For these participants, demographic, clinical, neurocognitive and neuropsychiatric data are presented in Table 1. In order to more widely investigate the possible relationship between SRS BOLD response and neuropsychiatric function we included *all* participants for this analysis, irrespective of performance accuracy threshold.

Pre-HD and symp-HD participants underwent gene testing prior to enrolment in the study and had CAG repeat length ranging from 39 to 50. All were clinically assessed using the Unified Huntington's Disease Rating Scale (UHDRS) motor subscale by clinicians (A.C or P.C). Following Tabrizi et al. (2009), HD participants were categorised as pre-HD if they had a UHDRS score of 5 or less (see Table 1). Years to onset of diagnostic motor symptoms were estimated via the parametric survival model outlined in Langbehn et al. (2004). All participants

were right handed (Edinburgh Handedness Test; (Oldfield, 1971)). Control participants were matched to pre-HD participants on age, gender and IQ (National Adult Reading Test 2nd edition, NART-2; (Nelson, et al., 1992)). As part of the IMAGE-HD protocol, all participants underwent a comprehensive neurocognitive and neuropsychiatric assessments, selected based on their sensitivity in previous large multi-site studies (Stout, et al., 2011, Tabrizi, et al., 2011). This included assessment of IQ, estimated from NART scores (National Adult Reading Test, (Nelson, et al., 1992)), cognitive function including SDMT (Symbol Digit Modalities Test; SDMT, (Smith, 1982)), Stroop word reading condition only; (Stroop, 1935), as well as assessment of neuropsychiatric symptoms via the SCOPI (Schedule of Obsessions, Compulsions and Pathological Impulses; (Watson and Wu, 2005)), FrSBe (Frontal Systems Behaviour Scale; (Grace and Mallory, 2001)), HADS (both anxiety and depression scales from the Hospital Anxiety and Depression Scale; (Zigmond and Snaith, 1983)) and BDI-II (Beck Depression Inventory Version II; (Beck, et al., 1996)). Additionally, we assessed odor identification via a 20 item modification of the UPSIT (University of Pennsylvania Smell Identification Test; (Doty, et al., 1984)). Motor speed and timing were assessed using speeded tapping and paced tapping tasks. Variance during speeded tapping (stap), reflected 1/inter-tap interval (ITI) while participants tapped a finger as rapidly as possible during repeated 10 second intervals. Paced tapping variability (1/ITI ptap), was assessed at 3 Hz by presenting a 3Hz tone with which participants tapped, then asking participants to continue tapping after the tone disappeared (Hinton, et al., 2007, Paulsen, et al., 2004). Symp-HD differed significantly from controls and pre-HD in age, SDMT, UPSIT, and paced tapping, and from controls only in Stroop and SCOPI checking, and from pre-HD only in UHDRS. Controls also differed from pre-HD in SCOPI

hoarding and HADS anxiety (see Table 1). Corresponding data for all participants (irrespective of SRS task accuracy threshold) is presented in supplementary Table S1.

[Table 1 about here]

Procedures

This study was approved by the Monash University and Melbourne Health Human Research Ethics Committees and written informed consent was obtained from each participant in accord with the Helsinki Declaration prior to enrolment in the study. All testing was undertaken at the Royal Children's Hospital, Parkville, Melbourne, Australia. Upon arrival at the hospital, participants completed the cognitive and neuropsychiatric testing, and practiced SRS task, after which they were positioned within the MRI scanner.

Shifting response set task

We adopted a modified version of the Loose et al. (2006) verbal response shifting. During each trial, a single letter (B, K or M) and a single number (2, 5 or 9) were simultaneously presented on either side of a central fixation cross (750ms). Trials were separated by a blank screen for 100ms. The task consisted of two conditions, the BASELINE condition and a more difficult ALTERNATE condition. During the baseline condition, participants responded by identifying which side of the central fixation cross contained the letter. During the alternate condition, the response set alternated between trials, requiring identification of letters, and then numbers, on each consecutive trial (i.e., continual switching between response sets). Stimuli were presented on computer screen with "Presentation" stimulus delivery software (Neurobehavioral Systems

Inc., USA), and responses recorded via a fibre-optic button box (Current Designs Inc., USA). We employed a blocked design, with the specific combinations of letter and number stimuli randomised between trials, blocks and conditions. Within each experimental session, participants completed four baseline blocks and four alternate blocks in sequential order (B A B A etc.). Each block lasted 28 seconds, and was identified by the word "letters" or "alternate" presented for 10.75 seconds immediately prior to each block. Participants completed two sessions, separated by a brief break in fMRI acquisition, providing 10.35 minutes of fMRI data. Response accuracy and reaction times (RT) were recorded.

[Figure 1 about here]

Neuropsychiatric Measures

All participants underwent a battery of assessments characterising clinical, neurocognitive, motor and neuropsychiatric function, as noted above. We conducted a factor analysis of motor measures and neuropsychiatric subscales to determine the principle features of disturbances in these domains. Analysis revealed three principle sources of variance within these measures, with the largest variance (factor 1) explained by executive dysfunction, disinhibition and apathy (FrSBE subscales), pathological impulses (SCOPI subscale), and the depression (HADS-D). Anxiety and obsessive compulsive subscales clustered on factor 2, while motor dysfunction uniquely clustered on the third factor. For this study we explored associations between SRS evoked BOLD responses and all neuropsychiatric subscales loading onto factor 1. Extracted factors are described in supplementary tables S3a and S3b.

fMRI data acquisition parameters

Structural and functional MR images were acquired on a Siemens Trio 3T MRI scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil. Echo planar images (EPI) were acquired in the axial plane (30 slices, 4 mm slice thickness, 1.8 mm x 1.8 mm in-plane resolution, TE = 35 ms, TR = 2250 ms, flip angle = 90°). Within each session, 138 functional volumes were acquired. High resolution T_1-weighted images were also acquired for registration (192 slices, 0.9 mm slice thickness, 0.8 mm x 0.8 mm in-plane resolution, TE=2.59 ms, TR = 1900 ms, flip angle = 9°).

Data Analysis

We performed a series of analyses. The first, based on a restricted subset of participants who met the SRS ≥70% accuracy threshold, was to characterise neural activity underlying executive functioning during SRS performance. For this analysis we report the main effects separately for each group, and also directly test for group differences. Next, we investigated associations between induced neural responses across *all* participants, within the previously identified regions of the prefrontal cortex, and measures of SRS performance (irrespective of task accuracy threshold) and neuropsychiatric functioning. It was important for this analysis to include poor task performers to allow full characterisation of associations between the integrity of prefrontal functional responses and cognitive (task accuracy) and neuropsychiatric disturbance.

SRS behavioural data analysis

Percentage accuracy in target identification and reaction time for responses were calculated separately for each task condition via one-way ANOVAs of accuracy scores for task condition

(baseline accuracy or alternate accuracy) across groups (control, pre-HD and symp-HD) (SPSS 19.0, IBM SPSS Statistics, Somers, NY, USA). Dunnett's t post hoc tests were used for individual group differences. These results are reported for the restricted set of accurately responding participants, and also for the total sample of all participants.

fMRI analysis: Neural correlates of shifting response set

All MRI data analysis was conducted with FSL software, version 4.1.7 (fMRIB, University of Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/). fMRI pre-processing and first level analysis was conducted via FEAT. Each session's 4D fMRI data were motion corrected (McFLIRT), employing brain extraction (BET), spatial smoothing (FWHM 5mm) and highpass filtering (143s cuttoff). Linear registration of functional data (6 degrees of freedom) utilised individual brain extracted T1 images, registered to standard space (canonical MNI 152T1 image) with 12 degrees of freedom. First level models included individual regressors, with temporal derivatives, for initial fixation periods, block instructions and the alternate condition (orthogonalised relative to instructions); the baseline condition was modelled implicitly. Movement parameters were not modelled, and the design matrix was prewhitened (FILM). Fixed effects (within session) contrast estimates of the alternate condition were combined at the second level for each subject, followed by third level estimation of mixed effects, including separate regressors for group (control pre-HD, symp-HD) and a single mean centered regressor controlling for differences in age (FLAME). Third level models were restricted to include only participants performing at or above 70% task accuracy, and third level contrasts specified one-tailed t-tests for the main effect within each group, and for pairwise group comparisons. At both the 1st and 3rd levels, we adopted the default z-score threshold of 2.3, with the additional cluster corrected p threshold of

0.05. One consequence of using a high level implicitly modelled baseline is that relative to responding with a consistent response set (i.e., identifying letters), shifting response set between trials is likely to be associated with regions of both significantly increased and decreased activity.

Per cent BOLD change within Regions of Interest

Our initial analysis identified regions of interest (ROI's) where neural responses facilitated accurate SRS performance. We next extracted BOLD time-courses from within ROI's across all participants irrespective of SRS performance accuracy. Hand drawn standard MNI space binary masks isolated cortical regions which contained activation clusters in the preceding analyses (main effects and group comparisons) were generated using FSLview. FEATquery then extracted per cent signal change scores during the alternate condition in each session, from within masked regions in subject space. The ROI included DLPFC [approximately BA 45 & 46, MNI centre ±36, 36, 28] within each hemisphere, dorsal ACC [approximately BA 32 & 24, MNI centre co-ordinate 0 16 40], subgenual ACC [approximately BA 24 & 25, MNI centre co-ordinate 0 12 -8] and the left anterior insula / frontal operculum [approximately BA13 &14, MNI centre co-ordinate -38 18 -4].

Associations between SRS performance accuracy, neuropsychiatric measures and neural response during the SRS task

We next examined how independent measures of cognition (i.e., SRS performance accuracy) and neuropsychiatric function (i.e., previously identified neuropsychiatric subscales) were associated with the SRS neural response. SRS performance accuracy was quantified as % change from

baseline condition. Associations are considered significant where $p<0.005$ (5 ROI's x 2 independent factors; SRS accuracy and selected neuropsychiatric ratings). Factor analyses confirmed SRS accuracy and selected neuropsychiatric subscales as independent sources of variance (see supplementary Tables S4a and S4b). We tested for both linear and quadratic relationships, and reported statistics for the association that best characterised the relationship in each case.

RESULTS

Behavioural performance during shifting response set

Participant groups, where accuracy was restricted to ≥70%, did not differ in terms of task accuracy; however, reaction times within each condition were significantly longer in symp-HD participants, compared with controls. Moreover, when groups were not restricted by accuracy threshold, symp-HD participants showed significantly lower performance accuracy, compared with controls and pre-HD groups, while reaction times significantly differed only between symp-HD and controls (see Figure 1 and Table 2).

[Table 2 about here]

Neural correlates of shifting response set

SRS was associated both with significant increases and decreases in BOLD signal, relative to the implicit, high-level baseline condition (i.e., consistently identifying letters). Activations during SRS performance were widespread, largely symmetrical within both cortical and subcortical regions, and similar across groups. In summary, we observed activity characterised by: 1) a

cognitive-attentional network comprised of prefrontal, parietal and dorsal ACC activity, 2) strong activity within the majority of the premotor cortex, 3) medial temporal lobe and basal ganglia activity, and 4) activation within the cerebellum (see Figure 2A and Table 3). Prefrontal activity included superior, medial, inferior and orbitofrontal gyri, with larger activation clusters within each group observed within the right hemisphere. Parietal activity approximately within Brodmann's area 7/40 was centred within the intraparietal sulcus, and traversed the majority of this sulcus laterally, and extended medially into the precuneous. ACC activity was observed within the dorsal "cognitive" region, and extended dorsally into motor regions. Activity within motor regions was restricted to the premotor cortical ribbon, and excluded the primary motor strip. Within the temporal lobe, anterior insula / frontal operculum activity was observed bilaterally, whereas within midbrain, activations were observed within all regions of the basal ganglia (dorsal caudate body, dorsal putamen and pallidum) and within thalamic nuclei, including the ventrolateral nucleus. Within the cerebellum, SRS activated both the vermis and superior cortical mantle, bilaterally. Significant activations are illustrated in Figure 2a, and are listed in Table 3.

In addition to activations, SRS was also associated with regional decreases in BOLD response (*or deactivations)*, relative to the implicit baseline condition. Again, these responses were broadly similar across groups, and characterised by reductions within: 1) medial prefrontal, subgenual ACC and orbitofrontal cortex regions, 2) posterior cingulate and precuneous deactivations, and 3) medial temporal lobe regions including the amygdala and parahippocampal gyrus, as well as regional deactivations within parietal and temporal cortical regions. Importantly, significant decreases in BOLD responses were also observed within basal ganglia

regions, including medial head of the caudate and ventral putamen. Significantly decreased BOLD responses during SRS are illustrated in Figure 2b, and are listed in supplementary Table S2.

[Table 3 about here]

fMRI Group differences in shifting response set

The majority of group differences were observed between control and symp-HD participants. Relative to controls, symp-HD participants showed significantly greater activations within dorsal ACC, superior and inferior frontal gyri, and within lateral orbitofrontal regions. Additionally, symp-HD participants showed significantly greater activations than controls within the left anterior insula, bilateral precuneous, right precentral gyrus and midbrain regions. These included the right dorsolateral caudate head, left posterior lateral and right anterior medial putamen, bilateral pallidum and thalamus (see Figure 2c and Table 4). Similarly, symp-HD participants also showed significantly greater deactivations during SRS when compared with controls. Larger reductions within symp-HD were observed within ventral prefrontal regions; namely medial orbitofrontal and subgenual ACC cortices, and surrounding ventral regions within the middle and inferior frontal gyri. Within basal ganglia regions, symp-HD had larger deactivations than control participants within ventral regions; namely the left ventromedial caudate head and the left anterior ventromedial putamen (see Figure 2D and Table 4).

Similar to symp-HD, pre-HD participants also displayed significantly increased activations compared with controls, all of which occurred within the left hemisphere. Significantly greater activations were observed within left frontal and temporal regions surrounding the insula cortex;

namely the left inferior frontal gyrus / frontal operculum, left superior frontal gyrus left anterior insula cortex, and left anterior precentral gyrus. Increased activations within pre-HD (relative to controls) were also observed within the basal ganglia, specifically within left dorsal caudate head, left anterior putamen and left anterior pallidum (see Figure 2c and Table 4). Symp-HD activity did not significantly differ from pre-HD.

[Figure 2 and Table 4 about here]

Associations between SRS performance accuracy, neuropsychiatric measures and neural response during the SRS task

We examined neural responses during the SRS task in specific ROI's for associations with SRS performance accuracy and neuropsychiatric subscales. For symp-HD participants, significant and negative associations were observed between increased DLPFC activity and deficits in SRS performance (within the left hemisphere), self-reported pathological impulses (SCOPI subscale) and depressive symptomatology (HADS- depression) within the right hemisphere, and executive dysfunction and dis-inhibition (FrSBe subscales) bilaterally. Executive dysfunction was also associated negatively with dorsal ACC and positively with subgenual ACC function (see Figure 3 and Table 5). Apathy (FrSBe subscale) however was not significantly correlated with evoked responses within any ROI. We observed no significant associations in control or pre-HD groups. Further post-hoc testing revealed no significant ROI associations with CAG length, DBS or UHDRS in pre-HD or symp-HD.

[Figure 3 and Table 5 about here]

DISCUSSION

We investigated the neural correlates associated with SRS performance within healthy controls, pre-HD and symp-HD participants, and observed exaggerated BOLD responses within both HD groups. Across all groups, accurate SRS performance was associated with increased activity within a matrix of cognitive-attentional regions, including widespread prefrontal regions, parietal cortex and dorsal ACC, as well as within the premotor cortex, medial temporal lobe, insula, basal ganglia and cerebellum. As hypothesised, accurate task performance was associated with significantly greater fMRI BOLD signal change in both pre-HD and symp-HD, compared with controls. Relative to controls, symp-HD showed significantly greater responses within many of the previously identified regions, including dorsolateral and inferior frontal cortices, dorsal ACC and basal ganglia (right dorsolateral caudate head and anterior medial putamen, left posterior lateral putamen, bilateral pallidum). Pre-HD participants also displayed significantly greater task associated activations than controls; however, these were restricted to left frontal and temporal lobe regions surrounding the anterior insula, and striatal regions including the left caudate, putamen and pallidum. Symp-HD participants also showed larger subgenual ACC reductions during SRS, compared with controls. Task related change did not significantly differ between pre-HD and symp-HD participants, and there were no regions where controls greater responses than pre-HD or symp-HD. Importantly, and as hypothesised, cortical responses correlated with SRS performance accuracy and with neuropsychiatric symptoms within symp-HD; that is, greater neural change during SRS was associated with increased performance accuracy and less neuropsychiatric disturbance. These findings illustrate, for the first time, the utility of imaging based measures in HD to identify exaggerated neural responses during accurate SRS performance. Further, these findings suggest that the failure to recruit compensatory neural

responses in symp-HD participants is associated with both poor task performance and self-reported neuropsychiatric disturbances.

Although cross-sectional, the pattern of results across premanifest and diagnosed groups suggests that as HD progresses, significantly increased prefrontal activity is required to maintain accurate performance. Our results are consistent with a "compensatory" interpretation of neural recruitment (Han, et al., 2009). That is, larger more widespread BOLD responses may reflect exaggerated localised neuronal activity and additional reallocation of cognitive resources to compensate for compromised cortico-striatal circuit integrity in symp-HD. Pre-HD participants also revealed increased compensatory responses, although across a smaller network of regions. Additionally, negative correlations in symp-HD revealed that as compensatory responses within left DLPFC failed, task accuracy diminished rapidly. Our findings are in accord with previous findings in HD demonstrating increased prefrontal activity during accurate task performance and decreased prefrontal responses with behavioural impairment. For example, Georgiou-Karistianis, et al. (2007) showed increased inferior frontal activity in symp-HD during accurate Simon task performance, relative to controls. Clarke et al. (2002) reported increased right middle frontal gyrus activity within pre-HD participants during successful Porteus maze navigation. Zimbelman et al. (2007) reported increased medial prefrontal and pre-central responses coupled with accurate paced motor performance in far from onset pre-HD, contrasted with reduced right inferior frontal responses in poorly performing close to onset pre-HD. Similarly, Kim et al. (2004) reported reduced middle frontal gyrus activity within pre-HD participants who failed to acquire implicit-learning rules. Moreover, in the studies by Wolf et al., while symp-HD participants with poor working memory performance displayed reduced left DLPFC (Ba 9)

responses (Wolf, et al., 2009), accurate working memory in pre-HD reflected increased right prefrontal (Ba 8) and reduced left DLPFC (Ba 9) responses.

Despite increased, presumably compensatory, right prefrontal responses in accurately performing pre-HD, the reduced left DLPFC response reported by Wolf et al., (2009) is initially puzzling and suggests that that DLPFC function may not be essential for the specific maintenance of working memory representations per se. While DLPFC activation during working memory tasks is commonly reported (Levy and Goldman-Rakic, 2000), the absence of working memory deficits within some DLPFC lesioned patients suggests a more general role (D'Esposito, et al., 2000). DLPFC function during working memory may instead inhibit distracting stimuli and inappropriate response options (Postle, 2006) consistent with a primary DLPFC role; inhibitory regulation of attention during the selection or maintenance of correct stimulus-response mappings. This is demonstrated by DLPFC responses underlying inhibition (Jonides, et al., 1998), executive attention (Kane and Engle, 2002, Mecklinger, et al., 2003), attentional monitoring and attentional selection (Passingham and Rowe, 2002, Petrides, 1994, Petrides, 2000a, Petrides, 2000b, Rowe, et al., 2005, Rowe, et al., 2000).

An important hypothesis was that prefrontal BOLD response during a challenge of cortico-striatal function would reflect neuropsychiatric disturbances in HD. As hypothesised, prefrontal SRS responses were significantly associated with self-reported neuropsychiatric disturbances within symp-HD participants. No significant associations were observed within control or pre-HD participants. In order to conduct this investigation, we investigated the most prominent cluster of neuropsychiatric symptoms within the available assessments (i.e., the factor explaining

the largest variance amongst our neuropsychiatric measures). While these measures did not in themselves differ significantly from controls, our investigation utilised inter-subject variability within symp-HD ratings to characterise specific associations with neural function. Of these subscales, all showed associations with prefrontal response except the FrSBe apathy scale. Despite clustering with other neuropsychiatric subscales, this may suggest a distinct neural basis for apathetic disturbances in HD. The strongest association observed was between executive function and right DLPFC response, with activity here additionally reflecting disinhibition, pathological impulses and depressive symptoms. In addition to SRS performance accuracy, left DLPFC also reflected executive dysfunction and disinhibition. Executive dysfunction was also reflected in the responsivity of the dorsal and subgenual ACC. In all cases, greater functional change within prefrontal ROI's was associated with less neuropsychiatric disturbance; conversely, left anterior insula function was not associated with any neuropsychiatric subscale investigated. It should be noted as a limitation, however, that some degree of caution should be applied when interpreting neuropsychiatric assessments solely based on self-report scales since a patient's perception of their difficulties may markedly differ from the perception of their relatives or caregivers.

Our finding, that induced functional responsivity within prefrontal regions additionally reflect neuropsychiatric function, is supported by previous studies in HD. For example, a number of studies have reported structural and diffusion changes in HD which correlated with clinical, motor, cognitive and neuropsychiatric status (Esmaeilzadeh, et al., 2011). Similarly, metabolic imaging research has also documented abnormalities in HD which have also correlated with cognitive and neuropsychiatric function (Bachoud-Levi, et al., 2000, Berent, et al., 1988, Deckel,

et al., 2000, Hasselbalch, et al., 1992, Hayden, et al., 1986, Kuhl, et al., 1982, Kuwert, et al., 1990, Leenders, et al., 1986, Mazziotta, et al., 1987, Smith, et al., 1988, Tanahashi, et al., 1985, Young, et al., 1986). Unlike these previous studies however, we investigated direct experimental challenge of prefrontal function underpinned by cortico-striatal circuits, and thus directly assess the functional responsivity within circuits associated with neuropsychiatric and behavioural disturbances. While associations between functional BOLD response and motor function have been previously reported (Georgiou-Karistianis, et al., 2007, Saft, et al., 2008, Wolf, et al., 2007), associations with neuropsychiatric status have received very little attention. Wolf et al (2008) provides the only previous report of an association neuropsychiatric status (indexed via UHDRS behavioural subscales) and BOLD response (inter-regional functional connectivity with left putamen). Our findings suggest that specifically targeting the inhibitory regulation of inappropriate response strategies via an SRS task provides a valuable index of functional integrity within neural circuits which are implicated more broadly in neuropsychiatric disturbance in symp-HD.

In summary, our results identify for the first time abnormally exaggerated fMRI BOLD responses during SRS performance in HD. Across those who met the performance accuracy threshold, symp-HD participants showed significant and more wide-spread compensatory increases in prefrontal function in order to maintain equivalent behavioural performance. Although there was evidence of compensatory increased activation in pre-HD participants, this was restricted to fewer regions. Further, and perhaps most interestingly, our findings suggest that a failure to recruit compensatory prefrontal responses in symp-HD is associated with reduced accuracy in SRS performance, and additionally with increased neuropsychiatric

disturbance. This finding suggests that prefrontal responsiveness during SRS performance could usefully index the functional integrity of cortico-striatal circuits within symp-HD. The functional integrity of compensatory responses within prefrontal circuits may provide a useful marker for development of treatments which aim to sustain cognitive function and delay executive and neuropsychiatric disturbance.

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Figure Legends

Figure 1. SRS task design and behavioural performance. A) Participants attend to one stimulus type only (baseline condition) or shift their attention between letters and numbers (alternate condition). B) SRS task performance with (left) and without (right) performance accuracy threshold. Error bars represent standard error of mean.

Figure 2. Neural correlates of shifting response set. A) Main effects within each participant group (alternate condition relative to implicit baseline). B) Between-group differences during SRS. Statistical parametric maps are displayed in radiological convention and overlaid on canonical MNI T1 image.

Figure 3. Associations between SRS performance accuracy, neuropsychiatric measures and neural response during the SRS task

% Δ Task Accuracy; % accuracy during baseline condition - % accuracy during alternate condition, FrSBe; Frontal Systems Behaviour Scale, R2 ; determinant of coefficient (unadjusted), b; standardised beta coefficient, Assoc; nature of strongest statistical association (either linear or quadratic), F statistics were calculated via ANOVA, p values are reported in BOLD when they pass our corrected threshold of alpha=0.005, and for completeness, associations at $p<0.05$ which do not survive correction for multiple comparison are also listed in grey. DLPFC: dorsolateral prefrontal cortex, ACC: anterior cingulate cortex, SCOPI: Schedule of Compulsions, Obsessions, and Pathological Impulses, FrSBe; Frontal Systems Behaviour Scale, HADS: Hospital Anxiety and Depression Scale. Associations illustrated are significant at $p<0.005$. No Significant associations were observed within controls or pre-HD participants.

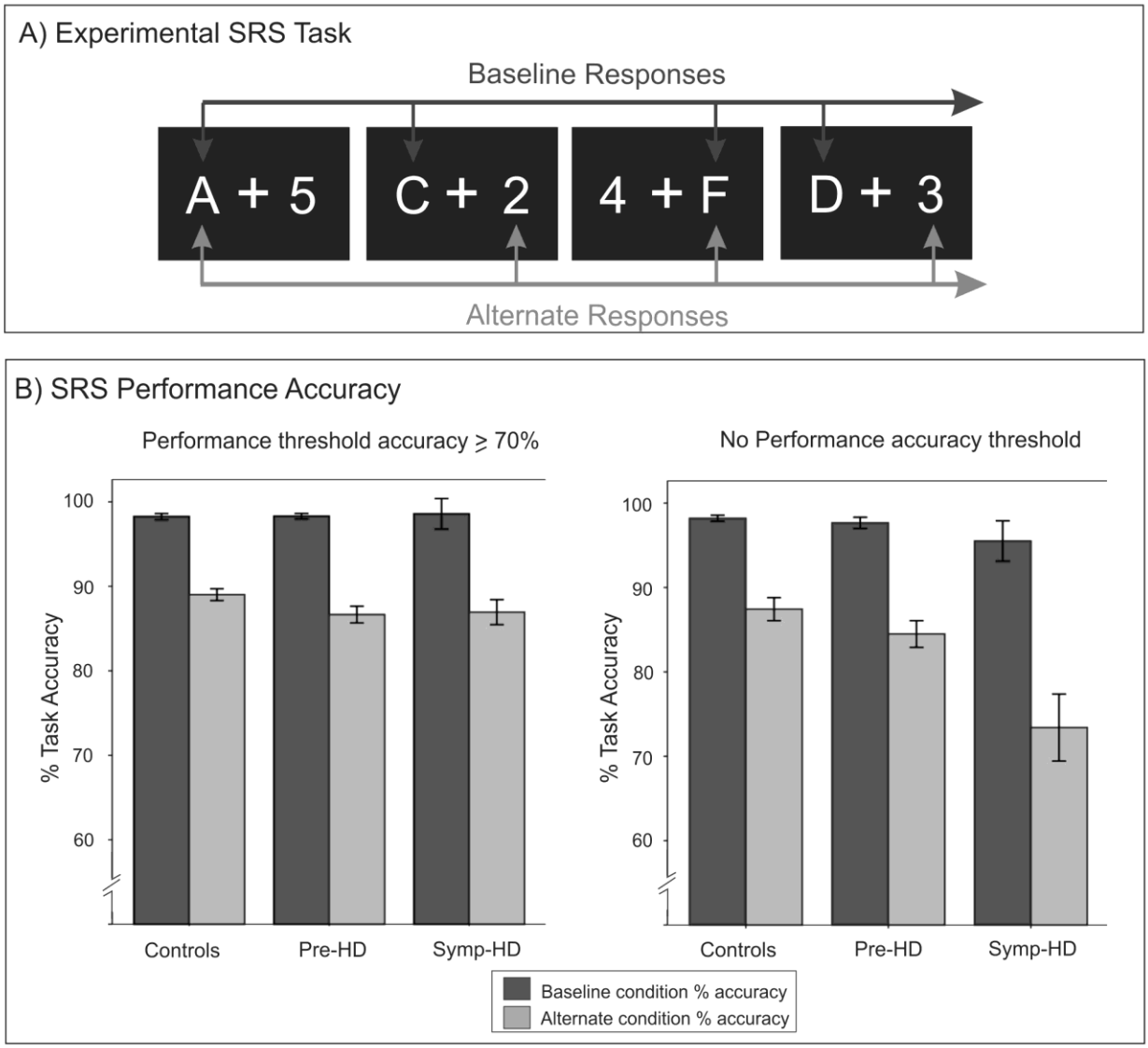

Fig. 1

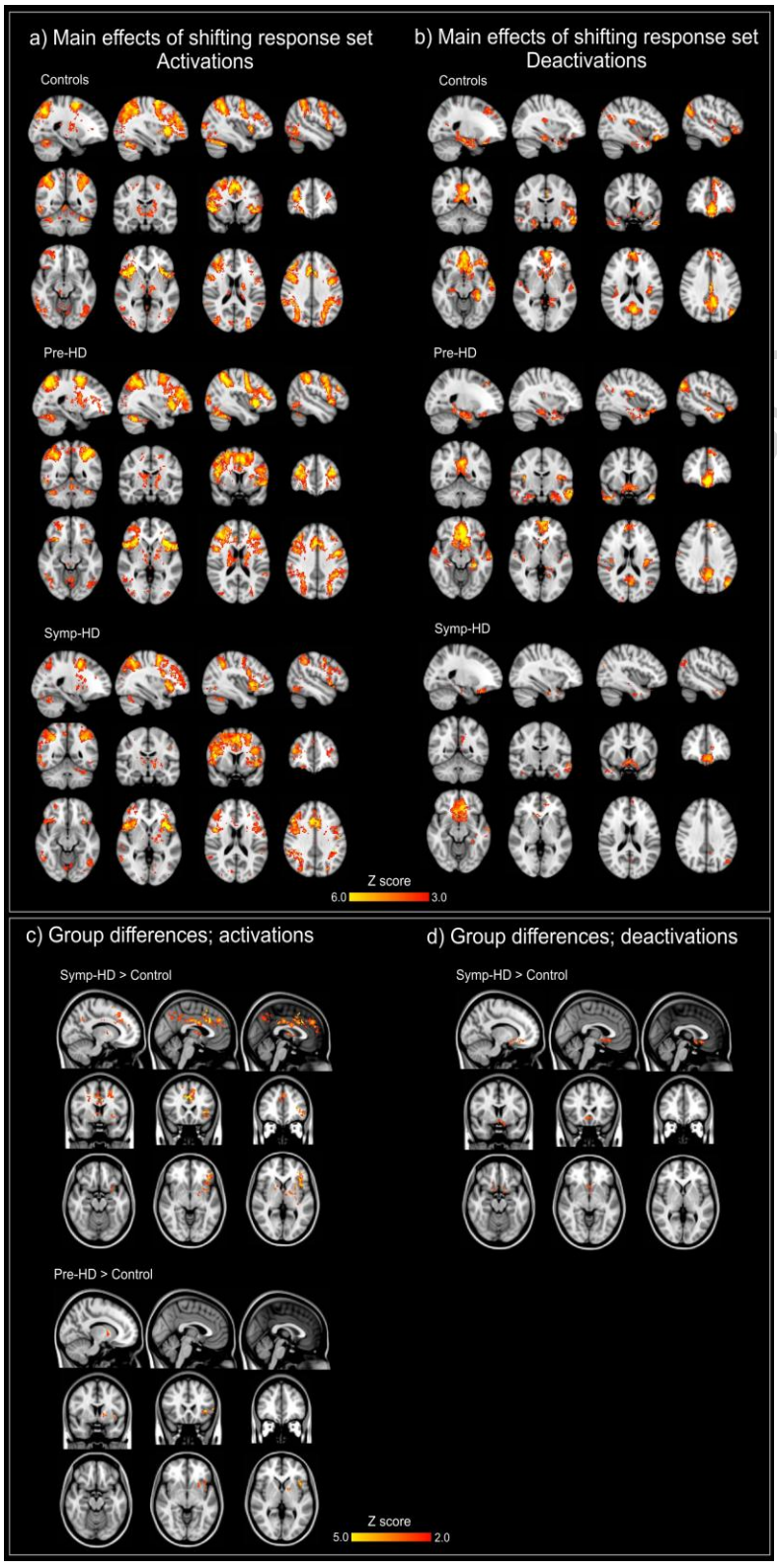

Fig. 2

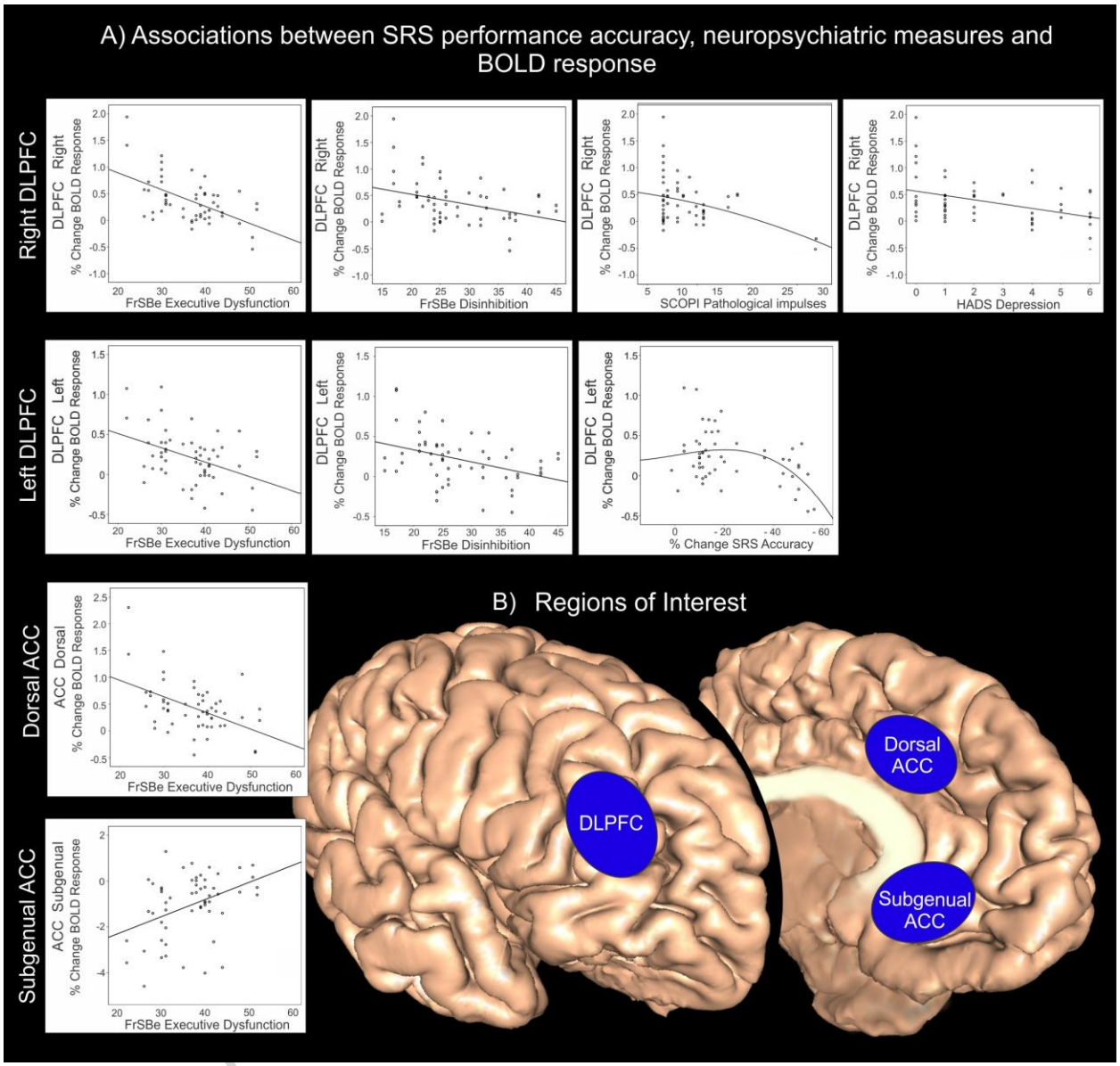

Fig. 3

Table 1. Demographic, clinical, neurocognitive, neuropsychiatric and motor information for participants performing at ≥ 70% SRS performance accuracy.

	Controls $\bar{x} \pm \sigma$	Pre-HD $\bar{x} \pm \sigma$	Symp-HD $\bar{x} \pm \sigma$
N	33	32	20
Age	37.0 ± 11.5 ●●	41.4 ± 9.9	46.4 ± 6.8 ×
UHDRS		0.0 ± 1.1	12.5 ± 6.4 ××
CAG		42.0 ± 2.1	43.0 ± 2.6
YTO		14.8 ± 8.1	
IQ	118.9 ± 9.9	116.9 ± 11.0	118.6 ± 10.2
SDMT	56.0 ± 9.2 ●●	49.0 ± 9.0 ++	43.0 ± 10.8 ××
STROOP	109.0 ± 16.6 ●●	103.0 ± 17.1	93.0 ± 17.5
SCOPI - total	82.0 ± 22.8	83.0 ± 25.4	86.5 ± 17.5
SCOPI - checking	30.0 ± 10.1 ●	35.0 ± 12.2	36.5 ± 8.5
SCOPI - cleanliness	27.0 ± 7.2	24.5 ± 8.6	28.0 ± 4.1
SCOPI - rituals	18.0 ± 6.5	16.5 ± 7.3	19.5 ± 6.1
SCOPI - hoarding	12.0 ± 4.0	15.5 ± 7.0 ++	9.5 ± 6.1 ××
SCOPI - pathological Impulses	11.0 ± 3.5	9.5 ± 4.0	11.0 ± 3.4
FrSBe - total	76.0 ± 26.0	92.0 ± 22.8	88.0 ± 18.4
FrSBe – apathy	23.0 ± 9.9	28.5 ± 8.5	27.5 ± 6.3

FrSBe – disinhibition	26.0 ± 7.4	26.0 ± 6.6	24.5 ± 7.1
FrsBe - Executive Dysfunction	30.0 ± 9.7	35.0 ± 10.1	36.0 ± 7.1
HADS - Anxiety	5.0 ± 2.8	6.0 ± 3.4 **++**	4.5 ± 3.9
HADS - Depression	2.0 ± 3.2	2.0 ± 3.0	2.0 ± 2.1
UPSIT	35.0 ± 3.2 ●●	34.0 ± 5.2	28.0 ± 6.7 ××
ITI stap	228.8 ± 69.7	244.7 ± 45.9	203.0 ± 39.1 ×
ITI ptap	23.8 ± 7.3 ●●	19.2 ± 7.7 **++**	11.3 ± 3.7 ××

UHRDS: Unified Huntington's Disease Rating Scale, YTO: Years to onset (Langbehn method), IQ: estimated from National Adult Reading Test, SDMT: Symbol Digit Modalities Test, Stroop: speeded reading, SCOPI: Schedule of Compulsions Obsessions and Pathological Impulses, FrSBe: Frontal Systems Behaviour Scale, HADS: Hospital Anxiety and Depression Scale, BDI-II: Beck Depression Inventory, UPSIT: University of Pennsylvania Smell Identification Test, ITI stap: Inter-trial interval in speeded tapping, ITI ptap: Inter-trial interval in self passed tapping.

●● Control Symp-HD $p<0.01$, ● Control Symp-HD $p<0.05$, **++** Control Pre-HD $p<0.01$, **+** Control Pre-HD $p<0.05$, **××** Symp-HD Pre-HD $p<0.01$, **×** Symp-HD Pre-HD $p<0.05$,

Table 2. SRS performance accuracy and reaction times across participant groups.

	Task Condition	Controls $\bar{x} \pm \sigma$	Pre-HD $\bar{x} \pm \sigma$	Symp-HD $\bar{x} \pm \sigma$
Performance Threshold (accuracy ≥ 70%)				
Accuracy	Baseline	98.26 ± 2.08	98.30 ± 1.82	98.59 ± 7.69
	Alternate	89.02 ± 4.02	86.66 ± 5.57	86.94 ± 6.27
Reaction Time	Baseline	469.6 ± 47.9 ●●	493.6± 72.1	528.6± 57.9
	Alternate	560.8 ± 74.9 ●	574.6 ± 90.4	641.8 ± 83.2
No Performance Threshold (all participants)				
Accuracy	Baseline	98.21 ± 2.11	97.66 ± 3.97	95.52 ± 12.40
	Alternate	87.43 ± 8.09 ●●	84.48 ± 9.36 ××	73.40 ± 3.97
Reaction Time	Baseline	474.0 ± 51.0 ●●	490.5 ± 71.0	536.7 ± 73.4
	Alternate	558.0 ± 75.4 ●	572.4 ± 88.1	615.2 ± 92.6

●● Control < Symp-HD $p<0.01$, ● Control < Symp-HD $p<0.05$, ×× Pre-HD < Symp-HD $p<0.01$, × Pre-HD < Symp-HD $p<0.05$,

Table 3. Neural correlates of shifting response set (Activations). Peak voxels are provided in MNI coordinates, activations are significant at $p < 0.05$ (whole brain cluster level correction).

Regions	Side	Controls				Pre-HD				Symp-HD			
		Peak Voxel			Z score	Peak Voxel			Z score	Peak Voxel			Z score
		x	y	z		x	y	z		x	y	z	
Orbitofrontal cortex lateral	L					-26	48	-12	4.27	-38	26	-12	4.15
	R	24	42	-14	6.73	20	50	-12	5.67	22	40	-18	4.98
Orbitofrontal cortex medial	L					-20	52	-12	3.86				
	R	16	50	-16	2.92	16	50	-16	3.70				
Anterior cingulate cortex	L	-6	16	44	7.85	-6	10	46	7.62	-2	10	46	8.36
	R	6	16	42	9.53	6	16	42	8.94	4	16	42	8.56
Superior frontal gyrus	L	-22	8	60	7.64	-22	8	60	7.30	-2	14	54	7.15
	R	26	8	56	8.09	24	4	58	9.64	0	16	54	6.13
Middle frontal gyrus	L	-4	14	48	8.89	-2	12	48	8.31	-2	12	48	7.62
	R	2	14	50	7.75	2	14	50	7.61	2	14	50	8.84
Inferior frontal gyrus	L	-44	4	32	8.46	-46	2	26	9.59	-46	2	30	8.09
	R	48	18	2	8.19	46	22	2	8.16	52	18	0	7.62
Superior temporal gyrus	L	-48	10	-4	6.36	-48	8	-2	7.51	-48	8	-2	5.59
	R	62	-42	20	5.23	50	12	-4	5.86	48	12	-4	6.30
Middle temporal gyrus	L	-30	-78	18	5.62	-46	-64	-4	4.68	-60	-62	-2	4.41
	R	36	-74	22	6.48	58	-48	-2	5.18	54	-54	-12	6.42
Insula	L	-30	18	8	9.43	-32	22	0	9.39	-32	20	0	9.32
	R	30	24	4	8.63	32	24	-2	8.71	36	16	6	7.98
premotor	L	-4	14	48	8.89	-2	12	48	8.31	-2	12	46	8.25
	R	4	6	56	7.77	10	16	44	7.64	2	14	50	8.84
Precentral gyrus	L	-28	-10	54	6.89	-40	0	32	8.94	-52	-8	40	7.58
	R	52	14	8	7.36	56	14	8	7.06	48	6	14	6.58
Superior parietal cortex	L	-24	-70	42	8.56	-24	-70	42	8.25	-10	-78	52	7.47
	R	14	-68	54	9.61	30	-66	50	8.89	36	-60	50	6.52
Inferior parietal cortex	L	-44	-46	42	10.04	-44	-44	42	9.84	-42	-42	36	8.26
	R	46	-38	46	8.50	48	-44	46	8.86	48	-44	38	6.27
Superior occipital gyrus	L	-24	-72	40	8.50	-24	-72	40	8.53	-12	-76	42	5.38
	R	22	-70	46	6.75	28	-80	36	6.97	30	-68	44	6.84
Middle occipital gyrus	L	-26	-76	38	7.93	-26	-66	30	7.32	-28	-76	32	7.36
	R	34	-76	32	7.12	32	-74	40	6.22	34	-76	32	6.21
Inferior occipital gyrus	L	-44	-84	-6	5.20	-46	-68	-18	5.89	-48	-70	-18	5.16
	R	40	-74	-8	5.80	38	-74	-8	5.18	40	-86	-2	3.87
Precuneus	L	-24	-70	42	8.56	-24	-72	40	8.53	-10	-78	52	7.47
	R	8	-70	52	9.20	8	-70	52	8.80	32	-70	42	6.56
Caudate	L	-16	-12	24	4.04	-16	16	6	3.77				
	R	14	-14	22	3.89	16	0	22	3.97	6	4	6	3.33
Putamen	L	-20	-4	14	4.32	-18	0	14	5.89	-26	6	2	5.43
	R	24	0	12	4.38	16	4	6	5.13	18	6	2	3.95
Pallidum	L	-22	-12	4	3.79	-16	-6	-6	4.90	-20	-4	2	4.42
	R	18	-6	0	3.18	14	4	2	4.02	16	4	-2	3.89
Thalamus	L	-8	-16	4	4.99	-14	-10	8	5.18	-10	-16	6	5.37
	R	14	-10	8	5.63	20	-22	16	5.41	18	-26	10	4.99
Cerebellum dentate	L	-34	-68	-26	8.58	-28	-70	-26	8.42	-30	-62	-22	6.59
	R	32	-66	-26	8.29	28	-62	-30	8.91	36	-68	-30	4.80
Cerebellum vermis		-6	-74	-24	8.13	-4	-74	-26	7.85	-6	-76	-24	4.67

Table 4. Group differences in shifting response set. Peak voxels are provided in MNI coordinates, activations are significant at $p < 0.05$ (whole brain cluster level correction).

Regions	Side	SRS Activations								SRS Deactivations			
		Symp-HD > Controls				Pre-HD > Controls				Symp-HD > Controls			
		Peak Voxel			Z score	Peak Voxel			Z score	Peak Voxel			Z score
		x	y	z		x	y	z		x	y	z	
Orbitofrontal cortex lateral	L	-38	26	-12	4.29								
	R									18	12	-18	2.76
Orbitofrontal cortex medial	L									-14	14	-20	3.89
	R									16	10	-18	3.10
Sub-genual anterior cingulate	L									0	22	-10	3.48
	R									4	14	-12	4.51
Dorsal anterior cingulate	L	-2	20	32	6.92								
	R	6	22	30	6.01								
Superior frontal gyrus	L	-2	14	54	4.69								
	R	18	14	54	4.24								
Middle frontal gyrus	L	-2	44	34	5.50					-10	32	-12	2.73
	R	4	56	22	4.54					12	24	-14	2.37
Inferior frontal gyrus	L	-38	26	2	5.73	-40	22	-2	5.95	-18	8	-20	2.43
Superior temporal gyrus	L	-48	18	-10	3.18	-44	10	-10	2.34				
Insula cortex	L	-38	16	0	6.37	-38	20	0	6.53				
Premotor cortex	L	-2	14	54	4.69								
	R	2	14	52	4.40								
Precentral gyrus	L					-44	18	10	2.64				
	R	30	-8	52	3.51								
Precuneus	L	-10	-58	32	4.06								
	R	2	-48	44	4.31								
Caudate	L					-6	8	8	3.68	-4	12	-6	2.45
	R	12	16	6	3.08								
Putamen	L	-30	-16	0	4.39	-24	12	-2	4.26	-12	6	-12	2.83
	R	16	12	-4	3.44								
Pallidum	L	-20	-4	2	3.21	-14	4	2	4.53				
	R	12	4	-4	2.64								
Thalamus	L	-8	-8	4	4.11								
	R	2	-12	8	2.71								

Table 5. Associations between SRS performance accuracy, neuropsychiatric measures and neural response during the SRS task.

	DLPFC (L)	DLPFC (R)	ACC Dor	ACC Sg	An Ins (L)
% Δ SRS Task Accuracy					
R^2	0.19	0.10	0.13	-	-
b	0.44	0.34	-3.56	-	-
Assoc	Q	Q	Q	-	-
F	12.36	6.80	7.53	-	-
p	0.001	0.012	0.008	-	-
FrSBe Executive Dysfunction					
R^2	0.15	0.28	0.22	0.14	-
b	0.41	0.54	0.49	0.40	-
Assoc	L	L	L	L	-
F	11.20	23.00	16.89	10.14	-
p	0.001	0.001	0.001	0.002	-
FrSBe Disinhibition					
R^2	0.13	0.12	0.11	-	-
b	-0.38	-0.37	-0.35	-	-
Assoc	L	L	L	-	-
F	9.52	8.94	7.89	-	-
p	0.003	0.004	0.007	-	-
SCOPI Pathological Impulses					
R^2	0.07	0.15	0.13	0.06	-
b	-0.27	-0.39	-0.37	0.28	-
Assoc	Q	Q	Q	L	-
F	4.38	9.73	8.23	4.64	-
p	0.041	0.003	0.006	0.036	-
HADS Depression					
R^2	0.09	0.15	0.1	-	-
b	0.33	0.41	0.34	-	-
Assoc	L	L	L	-	-
F	6.79	10.80	7.22	-	-
p	0.012	0.002	0.01	-	-

% Δ Task Accuracy; % accuracy during baseline condition - % accuracy during alternate condition, FrSBe; Frontal Systems Behaviour Scale, R^2 ; determinant of coefficient (unadjusted), b; standardised beta coefficient, Assoc; nature of strongest statistical association, either linear (L) or quadratic (Q), F statistics were calculated via ANOVA, p values are reported in black when they pass our corrected threshold of alpha=0.005, and for completeness, associations at $p<0.05$ which do not survive correction for multiple comparison are also listed in grey. DLPFC: dorsolateral prefrontal cortex, ACC Dor: dorsal anterior cingulate cortex, ACC Sg: subgenual anterior cingulate cortex, An Ins: anterior insula cortex, SCOPI: Schedule of Compulsions, Obsessions, and Pathological Impulses, FrSBe; Frontal Systems Behaviour Scale, HADS: Hospital Anxiety and Depression Scale. Associations illustrated are significant at $p<0.005$. No significant associations were observed within controls or pre-HD participants.

Prefrontal activity in Huntington's Disease reflect cognitive and neuropsychiatric disturbances

Journal Highlights:

- Symp-HD displayed increased compensatory BOLD responses while shifting response set
- Symp-HD prefrontal BOLD responses reflected cognitive and neuropsychiatric function
- Shifting response set in symp-HD is informative of generalised cognitive disturbance

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