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Functional imaging in Huntington's disease

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Abstract

Huntington's disease (HD) is a genetic brain disease characterized by loss of capacity in movement control, cognition, and emotional regulation over a period of about 30 years. Since it is well established that clinical impairments and brain atrophy can be detected decades prior to receiving a clinical diagnosis, functional neuroimaging efforts have gained momentum in HD research. In most brain disorders, there is accumulating evidence that the clinical manifestations of disease do not simply depend on the extent of tissue loss, but represent a complex balance among neuronal dysfunction, tissue repair, and circuitry reorganization. Based upon this premise, functional neuroimaging modalities may be more sensitive to the earliest changes in HD than are structural imaging approaches. For this review, PET and fMRI studies conducted in HD samples were summarized. Strengths and limitations of the utilization of functional imaging in HD are discussed and recommendations are offered to facilitate future research endeavors.

Keywords

Huntington's disease; Functional imaging; PET; fMRI

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by loss of capacity in movement control, cognition, and emotional regulation over a period of about 30 years. Recent reports suggest that clinical characteristics can be documented about 15 years prior to receiving a clinical diagnosis of manifest disease (Paulsen et al., 2008) and results in death approximately 15 years following motor diagnosis (Gusella et al., 1996). HD is caused by an expansion of a trinucleotide cytosine-adenine-guanine (CAG) in the 5'-translated region of the IT15 gene on the short arm of chromosome four (Huntington's Disease Collaborative Research Group, 1993) and length of CAG expansion is inversely correlated with age at diagnosis (Duyao et al., 1993). The characteristic pathological finding in HD is a loss of small to medium size spiny neurons, beginning in the dorsal medial head of the caudate with subsequent progression to the ventrolateral striatum (Gutekunst et al., 1999 and Vonsattel and DiFiglia, 1998); with less pronounced neuronal loss in other subcortical and cortical structures (Myers et al., 1991).

Over the past 20 years, the majority of HD imaging has exploited the use of structural imaging first using computed tomography (CT) and then magnetic resonance imaging (MRI). Measures of structural neuroimaging in symptomatic HD have been shown to be related to disease duration, severity of dementia, severity of movement disorder, cognitive performance, functional capacity (Rosas et al., 2008, Sax et al., 1983, Starkstein et al., 1988 and Starkstein et al., 1992) and even longer CAG repeat lengths (Aylward et al., 1997 and Rosas et al., 2001). Furthermore, basal ganglia volumes correlate positively with time to estimated diagnosis (Aylward et al., 1996) in persons with the HD gene-expansion who do not currently meet criteria for manifest disease, hereafter referred to as "pre-HD". Brain

atrophy has been shown to be evident decades prior to diagnosis in pre-HD (Paulsen et al., 2008).

Since it is established that much cell death has already occurred at the time of diagnosis (e.g., > 50%) (Aylward et al., 2004) and that cognitive, sensory, and psychiatric abnormalities often precede motor symptoms in HD (Duff et al., 2007, Paulsen et al., 2006 and Solomon et al., 2007), functional neuroimaging efforts have gained momentum in HD research. Whereas structural imaging provides static images of the brain, functional neuroimaging modalities such as positron emission tomography (PET) and functional MRI (fMRI) provide dynamic images of brain function. It has been hypothesized that neurons endure a period of neuronal dysfunction prior to death. Therefore, structural imaging characterizes brain volume and cell loss whereas functional imaging portrays brain performance and cell dysfunction. In most brain disorders, there is accumulating evidence that the severity of the clinical manifestations of disease does not simply depend on the extent of tissue destruction, but rather represents a complex balance among neuronal dysfunction, tissue repair, and circuitry reorganization. Based upon this premise, functional neuroimaging modalities may be more sensitive to the earliest changes in HD than are structural imaging approaches. Most functional imaging approaches used in HD have involved hemodynamic techniques that investigate neural activity by measuring changes in blood flow. Although issues remain to be resolved (Tagamets and Horwitz, 2001), it is generally agreed that blood flow is a good index of neural activity. Thus, we briefly review the use of noninvasive hemodynamic functional imaging techniques (PET and fMRI) in HD.

PET in HD

Kuhl and his colleagues (Kuhl et al., 1984, Kuhl et al., 1985 and Kuhl et al., 1982) published the pioneering studies of functional imaging in HD using PET with ^{18}F -fluorodeoxyglucose (FDG) and reported a decrease in glucose utilization that precedes tissue loss measured by structural imaging in all of their diagnosed HD and half of their pre-HD subjects. Findings were replicated and extended by many groups who reported that abnormal FDG uptake was associated with clinical measures of motor abnormalities and functional capacity and could be used to confirm genetic testing (Hayden et al., 1987, Mazziotta et al., 1987, Young et al., 1986 and Young et al., 1987). Findings from PET studies converged to challenge the concept that HD was of purely subcortical origin since glucose reduction was consistently reported in cortical as well as striatal regions of the brain (Goldberg et al., 1990 and Kuwert et al., 1990). Hypometabolism in cortical regions can be related to cortical abnormalities as well as functional deafferentation from subcortical regions, however, so the sequence of disease progression could not be clarified by these methods. Longitudinal FDG studies have shown change rates of 6.9 to 12.4% in diagnosed HD (Ciarmiello et al., 2006).

As concepts of basal ganglia connectivity became better characterized (Albin et al., 1990 and Alexander et al., 1986), PET studies used the radioactive tracers ^{11}C -raclopride, ^{18}F -fluoroethylspiperone, ^{11}C -methylspiperone (antagonists of D2 receptors) and ^{11}C -SCH 23390 (antagonist of D1 receptors) to examine dopaminergic receptor binding in HD patients. These ligands are used to reveal the neuronal loss in the striatum of HD since it is well-known that the medium spiny neurons specifically affected by HD bear these receptors. At least ten publications have used D1 and D2 receptor ligands in HD and results suggest that these PET measures show change over time that is sometimes (but not always) associated with clinical manifestations of disease, such as functional capacity and motor abnormalities. Although the published findings helped make it clear that PET was useful as a tool to elucidate neuropharmacology and clinical correlates of the basal ganglia, some researchers even envisioned a role for PET as a biomarker for HD. Longitudinal PET findings using dopamine receptor ligands in HD suggest mean annual changes of 4.8 to

5.2% for diagnosed HD (Pavese et al., 2003). Feigin and his colleagues Feigin et al., 2001 and Feigin et al., 2007 reported change scores up to 10% using a network approach that suggested different clinical and imaging measures may be needed for different phases of HD. Several studies examined PET correlates of cognitive, choreic and akinetic-rigid phenotypes of HD (Backman et al., 1997, Ginovart et al., 1997, Hagglund et al., 1987, Lawrence et al., 1998, Leenders et al., 1986, Sedvall et al., 1994 and Turjanski et al., 1997). Backman and Farde (Backman et al., 1997) conducted an overview of dopamine and cognitive functioning using PET findings in HD as an impetus. Conclusions emphasize that multiple measures of pre- and postsynaptic dopaminergic biochemistry are highly interrelated and strongly associated with cognitive deficits in HD, although speculation of whether D1 or D2 receptors are preferential markers in HD remains unclear.

Although fewer in number, benzodiazepine receptor binding was also measured in HD (using ^{11}C Flumazenil) since postmortem studies of HD have revealed large decreases in GABA (Perry et al., 1973). Findings in pre-HD and diagnosed HD (Holthoff et al., 1993 and Kunig et al., 2000) suggest that reduced striatal metabolism using ^{11}C Flumazenil may be evident later in the disease than that shown with FDG and raclopride. Authors interpreted these findings as evidence for a compensatory striatal GABA receptor upregulation in patients with manifest HD that is lacking in pre-HD.

PET in Pre-HD

We located well over a dozen studies using PET in at-risk HD participants who were not yet showing signs of a manifest movement disorder (i.e., pre-HD). Findings published before the location of the HD gene in 1993 were somewhat inconsistent, although three studies out of four studies still reported a significant glucose metabolism deficiency in pre-HD (Hayden et al., 1986, Kuwert et al., 1990, Mazziotta et al., 1987 and Young et al., 1987). Since the publication of the HD gene, however, it has become well established that several PET measures in pre-HD are abnormal prior to receiving a diagnosis of manifest motor disease, including D1 and D2 receptor binding, glucose metabolism (Andrews et al., 1999, Antonini et al., 1996, Ciarmiello et al., 2006 and Weeks, 1996); as well as the identification of a discrete pattern of altered functional brain circuitry referred to as the “HD-related metabolic network” (Feigin et al., 2001 and Feigin et al., 2007). Four PET studies in pre-HD reported longitudinal data with changes in striatal dopamine receptor binding ranging from 2.7% to 6.5% decrease per year, glucose metabolism diminishing by 2.3% to 7.6% per year, and increases in the HD-related metabolic network changing by an estimated 10.9% per year (Andrews et al., 1999, Antonini et al., 1996, Ciarmiello et al., 2006 and Feigin et al., 2007).

To our knowledge, there are very few published PET studies designed to elucidate brain activation associated with specific cognitive processes in HD. Not surprisingly, the two studies found for this review emphasized motor processing (Bartenstein et al., 1997); (Feigin et al., 2006). Bartenstein and his colleagues (1997) conducted an elegant study of voluntary movement in HD. Findings showed impaired activity of the striatum and its frontal motor projections areas with enhanced activity of parietal motor related areas. Authors interpret the diminished activations as a dampening of all output channels of the basal ganglia-thalamo-cortical motor circuit projecting to the cortex. The increased activations are construed to reflect compensatory recruitment of additional accessory motor pathways involving cortical regions helpful in conducting the motor task. Similarly, Feigin et al., (2006) showed that activation responses during motor learning were abnormally increased in the thalamus and orbitofrontal cortex, possibly to compensate for caudate dysfunction in pre-HD. Although there are other cognitive activation studies in HD, they used a different imaging modality, functional magnetic resonance imaging, or fMRI.

fMRI in HD

First introduced in the 90s, fMRI has been increasingly used to study brain function and to define abnormal patterns of brain activations resulting from HD. Compared to PET, fMRI is less expensive, less invasive, provides both structural and functional information, and allows event-related paradigms to study cognitive processing. Disadvantages include that fMRI is more sensitive to motion artifacts, is more difficult to apply to paradigms involving overt speech or auditory stimulation, and complicates interpretations of activations in orbito-frontal and anterior temporal regions due to susceptibility artifacts (for example, Schacter and Wagner, 1999). Excellent reviews of methodological and conceptual issues in functional imaging are available (Brown and Eyler, 2006 and Cabeza and Nyberg, 2000).

Six publications examined fMRI in diagnosed HD using various cognitive paradigms including maze learning (Clark et al., 2002), clock reading (Dierks et al., 1999), the response conflict Simon task (Georgiou-Karistianis et al., 2007 and Thiruvady et al., 2007), serial reaction time (Kim et al., 2004) and working memory (Wolf et al., 2008a and Wolf et al., 2008b). Not surprisingly, most have shown impaired task performance as well as significantly lower task-related activations in several subcortical and cortical regions (Kim et al., 2004, Wolf et al., 2008a and Wolf et al., 2008b). More compelling is the widely demonstrated finding of enhanced activation in various cortical areas (Clark et al., 2002, Dierks et al., 1999 and Georgiou-Karistianis et al., 2007) most often interpreted as cortical recruitment as a compensatory mechanism for task performances typically activated by dysfunctional brain areas.

Only one study prior to Wolf et al., 2008a and Wolf et al., 2008b, examined functional connectivity, defined as correlations of fMRI blood-oxygen level-dependent (BOLD) signal responses between brain regions (Thiruvady et al., 2007). Functional connectivity identifies regions that are synchronously active independent of task manipulations. In contrast with fMRI activation studies, which focus only on activation within individual brain regions, functional connectivity can determine inter-regional relationships (Friston et al., 1994 and Horwitz and Glabus, 2005). Thiruvady et al. (2007) (Thiruvady, et al., 2007) showed that HD patients had impaired functional connectivity between anterior cingulate and lateral prefrontal regions and that poor task performance was associated with the reduced connectivity.

fMRI in pre-HD

Five studies have used fMRI to examine brain function in pre-HD using time discrimination, global local interference (Paulsen et al., 2004a, Paulsen et al., 2004b and Reading et al., 2004), time production (Zimbelman et al., 2007), and working memory (Wolf et al., 2007). Findings consistently show that pre-HD participants with normal cognitive performances and no evidence of striatal atrophy show increased activations in cortical brain regions during task performance (Paulsen et al., 2004a, Paulsen et al., 2004b, Reading et al., 2004 and Wolf et al., 2007). This finding is typically interpreted as recruitment of cortical brain regions for maintenance of normal cognitive performances. Findings from pre-HD participants who demonstrate either striatal atrophy on structural MRI analyses or cognitive deficits, however, show more varied findings on fMRI. These findings include reduced activations in striatum (Paulsen et al., 2004a and Paulsen et al., 2004b), cingulate (Reading et al., 2004), or striatum and frontal regions (Zimbelman et al., 2007) as well as increased activations in fronto-parietal cortex (Wolf et al., 2007). A closer examination of these mixed findings suggests that varying findings likely reflect variation in the subject samples across the studies. For instance, the group estimated as “close” to diagnosis in the Wolf et al. (2007) paper has a much lower CAG repeat length (43.9 ± 3.0) than those considered “close” to diagnosis in the Paulsen and Zimbelman papers (48.2 ± 6.2). Consequently, the estimated

time to diagnosis in the former paper is more likely to be greater than that in the latter two papers. As a consequence it is possible that the different subsamples reflect different times in the transitional epoch of early HD disease where neural dysfunction begins to manifest in terms of cognitive deficit and striatal atrophy (see Paulsen et al., 2008 for curves of estimated disease manifestation).

Wolf et al., 2007 and Wolf et al., 2008b) published the only known study of functional connectivity in pre-HD. Using a working memory task, memory-related patterns of functional connectivity were shown by both healthy controls and pre-HD. Compared with controls, however, the pre-HD exhibited lower functional connectivity in left lateral prefrontal, parietal, and bilateral putamen regions that were associated with several aspects of HD. The identified functional networks were not confined to frontostriatal pathways but included frontoparietal networks with sparing of the striatum. This finding was emphasized as evidence for a primary cortical (vs. subcortical) role in the underlying mechanisms of HD. Although the authors speculate this pivotal role of the lateral prefrontal cortex in the pathophysiology of HD the sequence of dysfunction in these circuits cannot be known from the presented data.

Summary and discussion

This overview of functional imaging in HD shows a convergence of findings suggesting that a disruption of multiple brain networks can be identified before overt brain atrophy and behavioral manifestations of disease. Even though the traditional hallmark of HD is striatal cell loss, functional imaging findings argue strongly that HD reflects cellular dysfunction in both cortical and subcortical areas well before cell death. Interestingly, deficits in neurophysiology and morphology as well as subtle abnormalities in clinical symptoms have been shown to precede the occurrence of manifest disease and neuronal death in animal models (Hickey and Chesselet, 2003a, Hickey and Chesselet, 2003b, Laforet et al., 2001, Murphy et al., 1999 and Pallier et al., 2007); and humans (Aylward et al., 1996, Ciarmiello et al., 2006, Gomez-Anson et al., 2007, Hanson et al., 2008, Paulsen et al., 2008 and Whitlock et al., 2007).

As recently emphasized by Wolf et al., 2007 and Wolf et al., 2008b), the identified functional networks were not confined to direct frontostriatal pathways, as often suspected in HD, but were widespread. These findings are in concert with other structural imaging findings demonstrating widespread cortical thinning (Rosas et al., 2005), increased cortical gray (Nopoulos et al., 2007), and white matter abnormalities (Beglinger et al., 2005 and Magnotta et al., 2008) in HD. Indeed, given evidence that the huntingtin protein (Httex) is expressed throughout brain development (Bhide et al., 1996), it is possible that HD reflects both developmental and degenerative processes. An ongoing controversy not solved by the current findings in neuroimaging, however, is whether cortical degeneration precedes or results from subtle striatal alterations in HD. As aptly put by Signer and Tobin (Tobin and Signer, 2000) “None of the available data addresses the issue of whether Httex causes dysfunction from within the affected cells (e.g. of the striatum or cortex) or from without ... The failure to resolve this uncertainty calls into question all attempts to establish a specific cellular model for HD pathogenesis and is one of the most pressing outstanding issues.” Although some authors interpret cortical imaging findings as evidence for its preeminence in the pathophysiology of HD, there remain some caveats to this conclusion.

There has been substantial progress in our understanding of corticostriatal circuitry in the past decade. With recent mappings of cortico-striatal and cerebellar-striatal circuits (Hoshi et al., 2005), much of our knowledge of brain-behavior relations continues to be revised. For instance, Clower et al., (2005) provided the first evidence that a major output nucleus of the basal ganglia, the substantia nigra par reticulata, projects to a region of posterior parietal

cortex. Thus, activations of fronto-parietal circuits in the Wolf paper do not rule out a role for the striatum. In addition, the putamen has been shown as a target of efferents from the amygdala (Kelly and Strick, 2004). These, as well as numerous other advancements, too detailed to cover here, provide ample support for the long-standing cognitive and emotional dysfunction we have seen in HD. None of the evidence thus far advocates a sequence of pathological events in the HD brain, although ongoing research is likely to illuminate the underlying processes responsible for the motor, cognitive and emotional manifestations of this devastating disease.

New approaches to functional imaging have been emerging more quickly than feasible for adequate reliability and validity studies to be conducted. The most common method used to understand brain activations associated with cognition has been to provide converging evidence from other analyses that support one's findings. This approach has a number of limitations, although the one most cited is selective attribution (i.e., not mentioning studies that don't support one's findings). Horwitz and Poeppel, (2002) argue that "the main limitation is actually that the complexity of the brain ... makes it extremely difficult to say whether or not two findings obtained using methods with different ... features do or do not agree", p.1. Cabeza and Nyberg, (2000) suggest that the future of functional imaging requires the harmonic development of three approaches to interpretation: local, global, and network. Although the local approach has been emphasized in much of the HD findings thus far, the network approaches have more recently been considered in HD (Thiruvady et al., 2007, Wolf et al., 2008a and Wolf et al., 2008b) and suggest that HD researchers are intent in maximizing new methods and modalities to better understand this complex disease. It is likely that ongoing attention to these and other new advances in imaging as well as careful attention to methodological aspects of imaging technology will continue to elucidate HD.

A second interpretive challenge for HD functional imaging depends on the established relationships between neural circuitry and measured PET or fMRI data. According to Tagamets and Horwitz, (2001) the relations between neural activity and functional imaging vary by site and circuit. For instance, there are differences among different cortical regions and subcortical areas dependent upon whether local circuits are dominated by excitatory or inhibitory recurrence and whether the afferent occurs directly or indirectly. Although experiments using computational modeling show a close correlation between neuronal excitation and imaging measures, the same cannot be said for neuronal inhibition. As inhibitory processes are often interrupted by disease and acquired brain injuries, the importance of ongoing research to better map neural and imaging outcomes is essential.

Finally, as a relatively new and exciting methodology, functional imaging requires that readers are informed about the management of known limitations such as the brain-vein problem, movement artifacts, and the possible impact of structural abnormalities on functional signal (Brown and Eyler, 2006). The papers reviewed in this brief overview varied greatly in their description of imaging methodology. Transparent and clear publication guidelines will assist the design and implementation of future hypothesis testing in HD imaging. In addition to methodological details of the imaging protocols, HD research would be optimized by the development of international consensus criteria on HD diagnosis and staging, particularly with regards to pre-HD.

Conclusions and recommendations

It is clear from this review that functional imaging has made clear and substantial impact on our understanding of HD. Findings show that tools from functional imaging guide investigations of the pathophysiology of HD (as well as elucidation of the basal ganglia in general) and provide possible markers of disease diagnosis and progression. Despite methodological limitations, findings from PET and fMRI are highly consistent. For instance,

the HD related PET pattern described by Feigin and his colleagues (Feigin et al., 2001 and Feigin et al., 2007) is highly consistent with the pattern of hyper- and hypoactivations demonstrated by fMRI studies. PET has been successfully used to document longitudinal changes in HD (Antonini et al., 1996, Ciarmiello et al., 2006 and Feigin et al., 2007); and similar longitudinal studies would be beneficial using fMRI in HD. Once functional imaging methods have demonstrated adequate replicability, functional imaging may become more widely used to monitor treatment (Bachoud-Levi et al., 2006, Gaura et al., 2004, Hauser et al., 2002 and Kremer et al., 1999). The following recommendations may facilitate the efficiency and dissemination of future research findings using functional imaging in HD.

1. The development of clear consensus-driven guidelines for reporting functional imaging data. Standardized approaches are not meant to stifle creativity but to allow comparison across studies. For example, standard reporting should include approaches used to address the brain-vein problem, movement artifacts, signal dropout, image distortion, temporal characteristics, and the impact of structural abnormalities on functional signal. Standard reporting of effect sizes greatly facilitates comparison among studies.
2. Structural imaging findings should be reported in every functional imaging study in HD to help determine the staging of the sample and to facilitate interpretation of functional activations.
3. Percent change has consistently been used to report the amount of change seen in longitudinal studies of HD. The striking paucity of test-retest reliability studies, however, limit confidence in change scores. All measures chosen for the assessment of clinical outcomes require rigorous validation and psychometric testing.
4. Clear rationale for ligand use and choice of cognitive activation paradigms needs to be provided. Since it is clear that abnormalities exist in nearly all HD and pre-HD samples using functional imaging technologies, it is not necessarily beneficial to produce studies showing impairment in yet “one more” cognitive task or “one more” radiotracer. Rather, research design should build on current knowledge and provide data to clarify either mechanisms of HD or the utility of functional imaging markers for disease diagnosis and/or progression. Effect sizes should be used whenever possible to compare among several candidate outcome measures.
5. To date, there are no formal criteria used to make a diagnosis of HD or pre-HD. Currently, it is typical to diagnose HD when “an unequivocal movement disorder is present in a person at risk for the disease”. Descriptions of HD cohorts would be improved with a more thorough and standard reporting of consensus-driven characteristics, such as CAG repeat length, current age, gender, education, handedness, diagnosis age (if given), UHDRS total motor score, UHDRS cognitive scores, time to estimated diagnosis using Langbehn (if not yet diagnosed). Comparison among research reports would be improved with the development of standard clinical reporting criteria.

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