Altered cortical processing of sensory input in Huntington disease mouse models

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ABSTRACT

Huntington disease (HD), a hereditary neurodegenerative disorder, manifests as progressively impaired movement and cognition. Although early abnormalities of neuronal activity in striatum are well established in HD models, there are fewer in vivo studies of the cortex. Here, we record local field potentials (LFPs) in YAC128 HD model mice versus wild-type mice. In multiple cortical areas, limb sensory stimulation evokes a greater change in LFP power in YAC128 mice. Mesoscopic imaging using voltage-sensitive dyes reveals more extensive spread of evoked sensory signals across the cortical surface in YAC128 mice. YAC128 layer 2/3 sensory cortical neurons ex vivo show increased excitatory events, which could contribute to enhanced sensory responses in vivo. Cortical LFP responses to limb stimulation, visual and auditory input are also significantly increased in q175 HD mice. Results presented here extend knowledge of HD beyond ex vivo studies of individual neurons to the intact cortical network.

1. Introduction

Circuit changes and synaptic dysfunction precede neurodegeneration in several adult onset disorders of movement and cognition, including Alzheimer, Parkinson’s and Huntington disease (HD; reviewed by (Selkoe, 2002; Schirinzi et al., 2016; Tyebji and Hannan, 2017; Cepeda and Levine, 2020)). The most common inherited adult-onset neurodegenerative disorder, HD, is a progressive disorder of movement, mood and cognition caused by a CAG triplet repeat expansion greater than 35 in exon 1 of the HTT gene, which encodes the protein huntingtin (HTT) (Cell, 1993). The monogenic inheritance facilitates generation of mouse models with high construct and face validity (Pouladi et al., 2013), and ability to identify gene-expansion carriers in the prodromal stage, enabling therapeutic intervention to delay onset of clinical symptoms. Although genetic approaches to reduce brain levels of HTT are under investigation in early-stage HD (Tabrizi et al., 2019), these may not restore synaptic and circuit function (Molero et al., 2016). A better understanding of the mutant HTT (mHTT)-induced mechanisms underlying early alterations in synaptic and circuit function is needed to develop effective treatment for these changes.

The earliest neuropathological changes of HD occur in the striatum and in the motor, limbic and associative regions of cortex, which project glutamatergic afferents to the striatum (reviewed by (Waldvogel et al., 2012; Bunner and Rebec, 2016)), providing input to the basal ganglia-thalamic-cortical loop that selects motor actions and regulates emotional and cognitive behaviours (Kreitzer and Malenka, 2008). Abnormalities in cortical-striatal communication that occur prior to neurodegeneration are well documented in mouse models of HD (Bunner and Rebec, 2016; Milnerwood and Raymond, 2010; Raymond et al., 2011; Plotkin and Surmeier, 2015), and may, in part, explain early motor incoordination and chorea. Notably, selective knock-down of mHTT in cortical pyramidal neurons ameliorates behavioural phenotypes and improves cortico-striatal synaptic function (Virlogeux et al., 2018; Wang et al., 2014; Estrada-Sánchez et al., 2015a; Estrada-Sánchez et al., 2015b). However, intra-cortical network connectivity and processing in early HD is less well studied.

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Although disorders of movement, impairments in learning, and emergence of behaviors associated with depression and anxiety are the subject of numerous studies in HD mice models, less is known about sensory processing. Many patients with HD experience symptoms associated with reduced awareness of their body in space (Labuschagne et al., 2016), and posterior cortical regions associated with visuo-spatial processing often show early thinning on MRI (Rossi et al., 2002). Auditory processing, especially sound source localization and understanding speech in the context of ambient noise, show deficits in HD patients (Profant et al., 2017), while older studies suggest sensory perceptual changes and abnormalities of sensory-evoked potentials (Oepen et al., 1982; Hayward et al., 1985).

To begin to investigate cortical signaling networks in HD, we use sensory stimulation to evoke cortical responses measured on a mesoscale level, using electrophysiological recording from multiple brain regions as well as voltage-sensitive dye imaging in vivo, in two different HD mouse models at 6 months of age when motor symptoms manifest (Slov et al., 2003; Peng et al., 2016). We find that both YAC128 and q175 mice demonstrate enhanced power in sensory responses compared to WT littermates, and ex vivo patch clamp recordings suggested increased NMDA receptor-mediated excitatory cortical activity contributes to this enhanced sensory response.

2. Results

Cortical sensory processing is not well-studied in HD mouse models; however, changes in cortical regions involved in sensory processing have been reported on structural MRI from prodromal HD gene-expansion carriers (Pini et al., 2020). We are interested in mapping cortical network activity on a wide scale and began by measuring the cortical response to a sensory stimulus because it is time-locked and can be analyzed with fast techniques such as in vivo electrophysiology and voltage-sensitive dye imaging to compare genotype responses with precision.

2.1. Response to limb sensory input in YAC128

To evaluate sensory input in YAC128 HD mice, local field potentials (LFP) were recorded in the primary forelimb sensory cortex (FLS1), barrel sensory cortex (BCS1) and motor cortex (M) of 6-month-old mice anesthetized with isoflurane to reduce activity related to voluntary behavior and movement artifacts. Depth of anesthesia was determined by burst suppression due to isoflurane and evaluated for each experiment to ensure equivalence between genotypes (Supplemental Fig. 1).

Brief subcutaneous electrical stimulation of the contralateral forelimb resulted in an increase in LFP power in FLS1 as shown in representative experiment mean wavelets of stimulation epochs (Fig. 1A WT and B YAC128). Instantaneous LFP power in theta (3 to 7 Hz), alpha (7.1 to 12 Hz), beta (12.1 to 30 Hz) and low gamma (30.1 to 50 Hz) frequency bands was calculated by Hilbert transform and normalized to the 2 s baseline period before stimulation (Supplemental Fig. 2, Fig. 1C - J).

Genotype summaries of the change in LFP power (area under the curve of the normalized group data for 1.5 s following the stimulus) showed a significant increase in YAC128 FLS1 compared to WT (Fig. 1E; FLS1: frequency $p < 0.0001$, F (3, 48) = 11.41, genotype $p < 0.0001$, F (1, 48) = 180.2, no interaction $p = 0.0019$ by 2way ANOVA with Sidák’s multiple comparisons test show in figure). Moreover, the increase in LFP power was not restricted to limb regions of the primary sensory cortex. Strikingly, BCS1 also showed increased change in alpha, beta and gamma LFP power in YAC128 compared to WT (Fig. 1F, G, H, LFP: frequency $p = 0.0004$, F (3, 48) = 7.273, genotype $p < 0.0001$, F (1, 48) = 47.15 and no interaction $p = 0.0925$, F (3, 48) = 2.268). In the motor cortex, the change in power in theta, alpha, beta and gamma frequencies were greater in YAC128 (Fig. 1L,M, frequency $p = 0.779$, F (3, 52) = 0.363, genotype $p < 0.0001$, F (1, 52) = 124.3 and no interaction $p = 0.379$, F (3, 52) = 1.047 by 2way ANOVA with Sidák’s multiple comparisons test).

Consistent with a widespread increase in the response to forelimb stimulation, hindlimb stimulation in YAC128 also resulted in a greater change in LFP power in FLS1 at all frequencies (Fig. 2 C–F; K: $p < 0.0003$, F (3, 48) = 7.685 for frequency and $p < 0.0001$, F (1, 48) = 218.4 for genotype and $p < 0.006$, F (3, 48) = 4.685 interaction by 2way ANOVA with Sidák’s multiple comparisons test). M cortex show increased theta and M and BCS1 both show increased alpha, beta and gamma LFP power over baseline in YAC128 compared to WT (G-J, L) following hindlimb stimulation (BCS1: frequency $p = 0.0005$, F (3, 52) = 7.045, genotype $p < 0.0001$, F (1, 52) = 64.39 and interaction $p = 0.0259$, F (3, 52) = 3.347; M: frequency $p = 0.005$, F (3, 52) = 4.806, genotype $p < 0.0001$, F (1, 52) = 199.5, no interaction $p = 0.9041$, F (3, 52) = 0.188 by 2way ANOVA).

2.2. VSDI response to limb sensory input in YAC128

To better determine the spatial extent of the cortex activated by limb stimulation, we used mesoscale voltage-sensitive dye (VSD) imaging through a large craniotomy exposing the cortical hemisphere contralateral to the stimulation. As previously described (Mohajerani et al., 2016), hindlimb stimulation resulted initially in discrete regional depolarization of primary (HLS1) and secondary (HLS2A and HLS2B) hindlimb sensory cortex in WT with a small expansion to mostly midline cortical areas (Fig. 3A). HLS1, HLS2A and HLS2B secondary sensory areas were functionally determined by the center of activation and used to estimate the position of other cortical areas based on coordinates from the Allen Brain Mouse Reference Atlas. The spread of hindlimb-evoked sensory responses across the cortical surface was markedly more extensive in YAC128 mice compared to WT. In general, this manifested as a large non-uniform expansion of the signal into additional areas such as primary BCS1 along with a longer lasting depolarization (Fig. 3A and B). Contralateral hindlimb stimulation in YAC128 mice elicited a transient wave of depolarization encompassing 21.87 $±$ 2.17 mm$^2$ (n = 5) of the cortical surface (defined as pixels with a ΔF/F response at least 5× baseline RMS noise) compared to a significantly smaller 6.85 $±$ 2.61 mm$^2$ (n = 4) response in WT mice ($p = 0.0029$, $t = 4.473$, df = 7 by 2-tailed unequal t-test).

The spatiotemporal spread of VSD signals in mesoscale imaging makes these data amenable to optical flow analysis (Mohajerani et al., 2013). This approach calculates velocity vector fields to quantify the speed and direction of motion (Afrasteh et al., 2017). In the context of our data, we can measure the trajectory, direction and speed of the spread of neural activity across the cortex, represented by changes in the brightness of pixels over time and space. We quantified VSD cortical dynamics with the Optical Flow Analysis Toolbox (OFAMM) (Afrasteh et al., 2017) (available at http://lcbbridgebraindynamics.com/ofamm/) which revealed an increase in trajectory length (HLS1: $p = 0.0247$, K$–$S D = 0.2198; HLS1: $p = 0.0238$, K$–$S D = 0.1773) and temporal speed (HLS1: $p < 0.0001$, K$–$S D = 0.4648; HLS1: $p = 0.0041$, K$–$S D = 0.2475) in YAC128 from both HLS1 and HLS2A in response to hindlimb stimulation (Fig. 3C). Secondary HL and FL areas, as well as primary and secondary barrel cortex also showed increased trajectory length (HLS2A: $p = 0.0075$, K$–$S D = 0.2189; HLS2B: $p = 0.0001$, K$–$S D = 0.3967; HLS2B: $p = 0.0075$, K$–$S D = 0.0075; BCS1: $p < 0.0001$, K$–$S D = 0.2893; 2: $p = 0.0031$, K$–$S D = 0.2314) and maximum temporal speed (HLS2A: $p < 0.0001$, K$–$S D = 0.7750; HLS2B: $p < 0.0001$, K$–$S D = 0.5614; HLS2B: $p = 0.0561$ (ns), K$–$S D = 0.1881; BCS1: $p = 0.0054$, K$–$S D = 0.3115; BCS2: $p < 0.0001$, K$–$S D = 0.6087) in YAC128 after hindlimb stimulation (Supplemental Fig. 3).

In contrast to hindlimb stimulation, responses to forelimb stimulation resulted in widespread cortical depolarization that did not significantly differ between genotypes: (18.78 $±$ 5.35 mm$^2$ (n = 5) and 21.68 $±$ 1.66 mm$^2$ (n = 4) in YAC128 and WT mice respectively; $p = 0.6554$, $t = 0.4660$, df = 7 by 2-tailed unequal t-test). However, HLS1, HLS2A and BCS1 depolarization in YAC128 all showed higher correlation with other
Fig. 1. YAC128 HD mice show an augmented response to forelimb stimulation.
A and B) Representative local field potential (LFP) wavelets in primary forelimb sensory cortex (FLS1) in a WT and YAC128 mouse with forelimb stimulation at time 0. Time course summary of the change in LFP power (μV²) in FLS1 in C) the theta, D) alpha, E) beta and F) gamma frequency bands normalized to baseline. Time course summary of LFP power in Barrel sensory cortex (BCS1) at G) alpha and H) beta frequencies and in Motor cortex at I) alpha and J) beta frequencies. Area under the curve (AUC) of change in LFP power in K) FLS1, L) BCS1 and M) Motor cortex. n = number of mice, results are shown as mean ± s.e.m. and ***p < 0.001, **p < 0.01, *p < 0.05.
Fig. 2. YAC128 HD mice show an augmented response to hindlimb stimulation. A and B. Representative LFP wavelets in FLS1 in a WT and YAC128 mouse with hindlimb stimulation at time 0. Time course summary of the change in LFP power ($\mu$V$^2$) in FLS1 in C) the theta, D) alpha, E) beta and F) gamma frequency bands normalized to baseline. Time course summary of LFP power in BCS1 at G) alpha and H) beta frequencies and Motor cortex at I) alpha and J) beta. Area under the curve (AUC) of normalized change in LFP power in K) FLS1, L) BCS1 and M) Motor cortex. n = number of mice, results are shown as mean +/- s.e.m. and ***p < 0.001, **p < 0.01.
Fig. 3. Voltage sensitive dye imaging of the cortex with limb stimulation reveals increase in the area activated, trajectory and speed of the spread of the response in YAC128 mice. A) Time series of cortical wide-field voltage-sensitive dye imaging (VSDI) signals ($\Delta F/F_0$), from the right hemisphere of representative wildtype (top) and YAC128 (bottom) mice, during contralateral hindlimb (HL) sensory-stimulation scale: 2 mm. Note evoked signals, reflecting neuronal depolarization, propagate more extensively across the YAC128 cortical surface. B) Cortical surface area activated following hindlimb stimulation in WT (grey) ($n = 4$) and YAC128 (blue) ($n = 5$) mice and time course of activation in cortical areas following stimulation at time 0 ms. Significant differences between genotypes of the peak response are indicated. C) Example images of VSD responses originating from primary sensory areas in response to hindlimb stimulation (left, scale: 1 mm). Pixel trajectory length and maximum speed in response to hindlimb stimulation were both increased in YAC128 compared to WT for hindlimb primary sensory area (top panels) and forelimb primary sensory area (bottom panels). *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
cortical areas during the 500 ms following hindlimb stimulation compared to WT as shown by seed-pixel correlation maps and regional correlation matrices (Supplemental Fig. 4A,B). In addition, correlation between cortical areas following whisker stimulation was abnormally high in YAC128 compared to WT, suggesting that other types of sensory stimulation are augmented in YAC128 mice (Supplemental Fig. 4C).

2.3. Synaptic events ex vivo in YAC128

In HD models, the cortex and striatum have an imbalance in excitation and inhibition with increased glutamate signaling at extrasynaptic NMDA-type glutamate receptors (NMDAR (Cepeda and Levine, 2020; Raymond et al., 2011)). Furthermore, HD stage-dependent changes in inhibitory and excitatory input to cortical pyramidal neurons have been reported in acute brain slice recordings from R6/2 and YAC128 HD mice (Cummings et al., 2009; Indersmitten et al., 2015). The augmented sensory response in 6-month-old YAC128 mice shown here could result from increased excitation or decreased inhibition in cortical circuits. To investigate these possibilities in acute brain slices, we conducted whole-cell voltage clamp experiments to measure excitatory and inhibitory synaptic responses in the sensory cortex of 6-month-old YAC128 mice. The cell capacitance and membrane resistance of layer 2/3 pyramidal neurons was similar in WT (n = 27 cells (9 mice), capacitance 98.9 +/− 7.93 pF; resistance 137.7 +/− 16.8 MΩ) and YAC128 (n = 27 (9), capacitance 104.2 +/− 9.23 pF, NS p = 0.66, t = 0.43, df = 52 by unpaired t-test; resistance 185.5 +/− 26.04 MΩ, NS p = 0.13, t = 1.53, df = 51). Excitatory postsynaptic currents (EPSCs) in layer 2/3 pyramidal neurons were evoked by a short train of 10
stimulations at 20 Hz with a microelectrode placed 300 μm ventral. NMDAR-mediated EPSC were isolated by holding the cells at +30 mV while blocking AMPAR with CNQX and GABA_B with PTX. There was no difference between genotypes in the amplitude of EPSCs evoked by 20 Hz train stimulation (Supplemental Fig. 5, p < 0.15 unpaired t-test, t = 1.11, df = 9). However, in many cases, we observed substantially large amplitude, slowly decaying evoked responses (defined as >5x mean event amplitude). These large events, which also occurred spontaneously, were sporadically evoked by train stimulation, in which case baseline EPSC responses were entirely obscured (Fig. 4A,B). In order to compare evoked EPSCs without large amplitude events, the lowest stimulation intensity required to evoke synaptic responses was used (not different than control genotypes). However, more YAC128 neurons than WT neurons showed these large amplitude events, that have previously been described as “NMDAR spikes” (Puleg-Polksky, 2015; Palmer et al., 2014; Mahfooz et al., 2016) (p = 0.94, Chi-square = 4.295, df = 1, n = 10 (6) YAC128 and n = 11 (7) WT) following minimal stimulation (Fig. 4A,B). Under basal conditions without glutamate spillover, YAC128 neurons showed a variable proportion of stimulation trials that evoked large events (Fig. 4C). When glutamate uptake was blocked by DL-TBOA (Fig. 4D and E), YAC128 neurons showed a greater increase in event amplitude (p = 0.003 Kruskal-Wallis ANOVA; n = 7 (6) WT and n = 8 (6) YAC128; with Dunn’s multiple comparisons in YAC128 control vs. TBOA *p = 0.03) and frequency (Kruskal-Wallis ANOVA, approximate p = 0.004 with Dunn’s multiple comparisons in YAC128 *p = 0.04,) compared to WT neurons (Kruskal-Wallis ANOVA as above, Dunn’s multiple comparison before vs after TBOA in WT p = 0.14 for frequency and p = 0.08 for amplitude).

In contrast to the difference in excitatory events seen in YAC128 layer 2/3 sensory cortex pyramidal neurons, spontaneous inhibitory postsynaptic currents (sIPSCs) from these neurons (recorded at +10 mV) showed similar frequencies and amplitudes in WT and YAC128 mice (Fig. 4F-H). Although WT and YAC128 Layer 2/3 pyramidal neurons showed similar sIPSC frequencies, reduced tonic GABA-mediated inhibition might also account for the enhanced sensory spread and has been reported in HD models (Wójcieszowicz et al., 2013). However, we did not observe a significant genotype difference in the holding current blocked by GABA_A receptor antagonist picrotoxin (50 μM) (percent change WT -16.00 +/- 6.22, n = 7 (3) and in YAC128-21.55 +/- 3.78, n = 11 (3), NS p = 0.43, t = 0.811, df = 16 by unpaired t-test). We also recorded miniature IPSCs in layer 5 pyramidal cells and found no significant difference between WT and YAC128 in either the mean frequency (WT 14.86 Hz +/- 1.28 vs 13.73 Hz +/- 1.68 YAC128, p = 0.59, t = 0.54, df = 22, by unpaired two tailed t-test with n = 13 (5) and n = 11 (5) (respectively) or amplitude (WT 54.13 pA +/- 5.34 vs YAC128 43.67 pA +/- 7.34, p = 0.25, t = 1.176, df = 22). Together, these data suggest an increase in excitatory input rather than altered inhibition to cortical layer 2/3 pyramidal neurons contributes to enhanced cortical spread of sensory responses in YAC128 mice.

2.4. Limb sensory input in zQ175

To determine if the altered sensory response observed in YAC128 mice was found in other HD mouse models, we measured LFP power in zQ175 HD mice. The level of anesthesia for these experiments was lower than that used in YAC128 mice (Supplemental Figure 1) to facilitate movement and also impair cognition, key areas of clinical decline in patients with HD. Here we report that cortical responses to sensory stimulation, as measured by in vivo brain imaging or electrophysiological approaches, are augmented in two HD mouse models, YAC128 and zQ175, compared to WT littermates. Multiple cortical areas were depolarized in YAC128 in contrast to the discrete spatial response in WT mice shown here by VSDI. Results for hindlimb stimulation as observed.
neuronal activity shown as probability of Multi-unit (MU) events in FLS1. Inset shows representative events and mean waveform for one experiment with scalebar.

B) representative wavelets from FLS1 in a WT and zQ175 mouse with hindlimb stimulation at time 0. C) Time course summary of FLS1 normalized alpha power in WT and zQ175 mice in the amplitude or frequency of sIPSCs recorded from sensory cortical neurons in the motor cortex showed a decrease in IPSC amplitude with stimulus acuity (Rumyantsev et al., 2020), the augmented cortical sensory processing is more dependent on alterations to network properties of cortical neurons in the HD brain. However, studies will investigate the mechanism of these events and their relation to sensory responses in vivo.

In addition to the increased spread of sensory-evoked VSD responses in YAC128 cortex, the optical flow analysis revealed a greater maximum temporal speed of signal propagation. Previous work has shown that sensory cortical neurons of R6/1 and R6/2 mice have increased input resistance, decreased cell capacitance, and a depolarized membrane potential at symptomatic ages (Cummings et al., 2009; Cummings et al., 2006). Cortical pyramidal neurons from YAC128 and CAG140 mice also exhibit increased input resistance starting at 6 or 12 months of age, but normal resting membrane potential and cell capacitance (Cummings et al., 2009). Although those previously published data suggest that changes to membrane properties of cortical neurons in the HD brain could explain the observed increase in propagation speed, our data show no significant difference in membrane capacitance or resistance in layer 2/3 cortical pyramidal neurons from 6 month-old YAC128 vs. WT mice.

Subthreshold signals in dendritic processes, which represent most of the neuronal surface area, appear to predominantly mediate the sensory-evoked activity of individual cortical neurons in relation to their relative anatomical positions. It is noteworthy to mention that we noticed a region- and stimulus-dependent variability in the spiking activity between animals that could result from the relative locations of cortical point spreads to the recording sites (Frostig et al., 2017).

Given that correlated noise over large cortical areas can decrease stimulus acuity (Rumyantsev et al., 2020), the augmented cortical sensory response in HD mice could be detrimental to performance of sensory-motor tasks and contribute to impaired motor learning. For instance, inhibition in the sensory cortex is important for hand grasping in humans (Lei et al., 2018), and HD patients may also exhibit deficits in reaching and grasping movements (Klein et al., 2011). Human MEG by VSDI and LFP recordings were remarkably complementary, with both methods showing augmentation of the sensory response by cortical dynamics in the HD model mice. The spread of sensory-evoked signals across the cortical surface (sensory-spread), measured with VSDI or other methods, has been documented in numerous mammalian species ranging from rodents to primates (Grinvald et al., 1994; Brett-Green et al., 2001; Petersen et al., 2003; Johnson and Frostig, 2018). This physiological role(s) of sensory-spread are incompletely understood (Grinvald et al., 1994; Brett-Green et al., 2001; Petersen et al., 2003; Johnson and Frostig, 2016). However, the widespread signals across the cortical surface, often irrespective of function boundaries, suggests diverse roles in cortical integration (Petersen, 2019; Svoboda and Li, 2018).

In WT animals the extent of the sensory spread (measured with VSDI) varied considerably with the modality tested. In contrast, YAC128 mice show consistently large areas activated, with the maximal hindlimb sensory spread more than triple that of WT. Consistent with this, coherence between cortical areas was greater in YAC128 than WT mice not only following hindlimb stimulation, but also whisker stimulation. Similarly, both YAC128 and zQ175 mice had greater responses to multiple sensory modalities compared to WT in motor and sensory cortical areas, including forelimb stimulation when responses were measured by recording local field potentials, which are more sensitive to high-frequency oscillations. BCS1 showed fewer significant differences between genotypes in LFP response to limb stimulation in YAC128 and in zQ175. This recording site was the most distal from the primary limb sensory areas and could be less impacted by sensory spread by this modality. In contrast, BCS1 in zQ175 showed differences from WT in all frequency bands in response to visual and auditory stimulation.

At the level of cortical synapses, impaired balance of inhibition and excitation could contribute to the increased sensory spread in YAC128. Sensory cortical spontaneous IPSCs are reduced in older symptomatic R6/2 mice and EPSCs are more frequent (Cummins et al., 2009; Nae et al., 2018). However, the same study showed an increase in IPSC frequency in the CAG140 and YAC128 models. Previous studies of neurons in the motor cortex showed a decrease in IPSC amplitude with an increase in frequency in 12 month-old q175 mice (Indersmitten et al., 2015). A decrease in inhibition in layer 2/3 of the motor cortex is also shown by in vivo calcium imaging and ex vivo immunohistochemistry in HD mouse models and patients (Burgold et al., 2019; Gu et al., 2005). These studies have shown conflicting results as to how inhibition is affected in the cortex in HD, and likely differ depending on the region studied. Here, in HD mice that exhibit aberrant sensory stimulus-induced activation of both the sensory and the motor cortex in vivo, our ex vivo experiments show no difference between WT and YAC128 mice in the amplitude or frequency of sIPSCs recorded from sensory cortex pyramidal neurons in layer 2/3 or of mIPSCs in layer 5. Moreover, we also found no difference in GABA_A receptor-mediated tonic current recorded from sensory cortex layer 2/3 pyramidal neurons in acute brain slices from YAC128 compared to WT mice. Although YAC128 mice at 6 months of age do show an HD-like phenotype and synaptic deficits, it is possible that a change in IPSCs occurs in older YAC128 mice.

Interestingly, cortical neurons in R6/2 mice show enhanced spontaneous, large amplitude “complex” events that increase in frequency and duration compared to WT as the mice age (Cummins et al., 2009; Indersmitten et al., 2015). Here we report that YAC128 neurons display larger amplitude events in response to stimulation of excitatory afferents than WT. Although the experimental conditions were different in the R6/2 study, it is striking that both HD models surprisingly exhibit large amplitude excitatory events. We and others have previously shown increased excitatory transmission and extrasynaptic NMDAR function in the striatum in HD models (Milerwood and Raymond, 2010; Raymond et al., 2011; Botelho et al., 2014; Plotkin et al., 2014; Kovalenko et al., 2018). The large amplitude events shown here are consistent with augmented extrasynaptic NMDAR-mediated events in the cortex of YAC128, since they increase with glutamate spillover and occur in the presence of AMPA and GABA_A receptor blockers. It is possible that these events occur due to network bursting and synaptic integration (Mahfooz et al., 2016) or by astrocytic release of glutamate following stimulation (Covelo and Araque, 2018). Astrocytes also contribute to hyperexcitability in the striatum in HD models, although fewer studies in HD models look at astrocytes in the cortex (Khakh et al., 2017). Future studies will investigate the mechanism of these events and their relation to sensory responses in vivo.
Fig. 6. zQ175 HD mice show an augmented LFP power in response to auditory and visual sensory input. A) Time course summary of LFP power at alpha frequencies in WT (black) and zQ175 (blue) FLS1 with a 10 ms blue led flash at time 0. B) Comparison of LFP power in FLS1 WT and zQ175 showing greater activation in all frequency bands. C) MU event probability increases after visual stimulation but shows no significant difference between genotypes. Inset shows waveforms with scalebar 50 μV and 0.5 ms. D and E) LFP power increase in response to visual stimulation and MU event probability in BCS1. F and G) LFP power increase and MU event probability in M1. H–N) zQ175 and WT LFP response to auditory sensory stimulation shown as above. Data shown as mean +/− s.e.m. *p < 0.05, **p < 0.01, ***p < 0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
studies show that suppression of gamma power in the visual cortex modulates reactions to sensory input (Orekhova et al., 2018), suggesting that increased gamma power in other cortical areas could also impair reactions to sensory input. It is interesting to note that sensory LFP responses in HD mice were consistently elevated in the gamma range in FLS1, M and BCS1. Similarly, aberrantly increased gamma oscillations in awake behaving mice have been shown in the cortex and striatum of the R6/2 mouse model of HD (Naze et al., 2018).

Taken together with the increased LFP response to visual and auditory stimulation in zQ175, our results showing enhanced VSDI and LFP response to limb stimulation demonstrate consistently aberrant cortical dynamics that generalize across HD models and sensory modalities. These results in conjunction with our ex vivo slice data suggest subthreshold synaptic depolarizations, perhaps mediated by increased extrasympathetic NMDA receptor expression, underlie the increased sensory spread in HD mice.

4. Methods

4.1. Animals

All procedures were performed in accordance with the Canadian Council on Animal Care and University of British Columbia Animal Care Committee regulations (approved under protocol A19–0076). Mice were group housed with 2 to 4 mice per cage on a 12 h light, 12 h dark cycle. Water and standard laboratory mouse diet were available ad libitum. Male YAC128 Line 53 and their wild-type FVB littermates (Slow et al., 2003), and zQ175DN mice (Southwell et al., 2016) (https://www.jax.org/strain/029928) and their wild-type C57/B6 littermates were implanted with electrodes at 5- to 6-month-old as below and allowed to recover for 1 to 4 weeks before experiments.

4.2. Electrode implant surgery

Mice were anesthetized with isoflurane at 3% for induction then reduced to 1.5 to 2% for stereotactic surgery. The eyes were covered with eye lubricant (Lacrilube; www.well.ca) and body temperature was maintained at 37 °C using a heating pad with a feedback thermistor. A skin flap extending over the dorsal cortex was cut and removed. Fascia or connective tissue was lightly scraped away from the skull and small (< 1 mm diameter) holes were drilled through the skull, using a high-speed dental drill with sterile bit, over the cortex. Twisted tungsten wire tetrodes (25 μm diameter, California Fine Wire Co.) – typically 3 – were directed toward the center of burr holes and placed in the cortex (depth: 500 μm) using a motorized micromanipulator (MP-225, Sutter Instrument Co.). Electrodes were implanted in the cortex at the following coordinates in mm relative to Bregma: primary forelimb sensory cortex (FLS1: AP 0.5, ML 2.25, DV 0.5), barrel sensory cortex (BCS1: AP 0.1, ML 3, DV 1) and motor cortex (M1: AP 1, ML 1.5, DV 0.5). Miniature connectors (2 × 2 × 2 mm) were cemented to the skull (with dental adhesive). Ground and reference electrodes (silver wire) were fixed onto the surface of the posterior skull. Prior to implantation, tetrodes were painted with fluorescent 1,1-dioctadecyl-3,3,3,3-tetramethylindocarbocyanine perchlorate (Dil, ~10% in dimethylfunarin, Molecular Probes, Eugene, OR) and the solvent allowed to evaporate. For histology, immediately following the experiment, animals were decapitated and the brain fixed in 4% paraformaldehyde. The brains were sliced on a vibratome and Dil labeling counter-stained with DAPI was used to identify the tetrode tract and confirm the approximate cortical location.

4.3. In vivo electrophysiology

Mice were anesthetized with 1–2% isoflurane and body temperature maintained at 37 °C with a heating pad and feedback thermistor (Harvard Apparatus). To stimulate forelimb and hindlimb, a 1 ms pulse of 0.5 - 1 mA was delivered by thin acupuncture needles (0.14 mm) inserted subcutaneously into the paw. In zQ175 experiments visual stimulation was a 10 ms flash of blue light and auditory stimulation was a 1 ms broad frequency spectrum ‘chirp’ produced by a TTL pulse to a Piezo Element (Adafruit). Responses were calculated from 10 to 20 trials of stimulation, each trial separated by 10s. LFP signal was recorded at 25 kHz and filtered (0.1 to 1000 Hz) using a 16-channel data acquisition system with a 1200 gain (USB-ME16-FAL-System, Multi Channel Systems or an RH2D132 amplifier chip and Intan recording controller). LFP power analysis of one tetrode wire from each area was performed in MATLAB (2019; Mathworks, Natick, MA). Isoflurane burst suppression was evaluated to ensure groups were at similar anesthetic levels by measuring the mean duration between bursts (Supplemental Fig. 1). If the level of anesthetic changed during the experiment, those stimulation trials were excluded from the analysis. The Morlet wavelets (6 cycle) of each epoch were averaged for visualization of the experiment. LFP recordings were band-pass filtered (Mathewson et al., 2014) for theta (3 to 7 Hz), alpha (7.1 to 12 Hz), beta (12.1 to 30 Hz) and low gamma (30.1 to 50 Hz) frequencies followed by isolating epochs of 2 s before and 3 s after stimulation with no bursting activity in the 200 ms before stimulation (automatically determined by an absolute value greater than 200 μV in the unfiltered data). 10 to 20 trials were analyzed for each experiment after exclusion criteria were applied as above. Hilbert transform for instantaneous power calculated (using the MATLAB function) for each individual trial epoch and the results averaged as shown in Supplemental Fig. 2. The change in averaged LFP power over the 2 s baseline prior to stimulation was calculated and then grouped by genotype and sensory modality and the area under the curve of normalized power was used for statistical analysis as below.

For multi-unit spike analysis, the raw signals were band-pass–filtered (300 to 3000 Hz), after which spike detection was performed in MATLAB (R2019a). The threshold for spike detection was set to 3.5-fold of the SD of a second-spike-free window of each recorded signal. As a quality control of the isolated multi-units, we inspected the shape of spike waveforms, and only the units with a clear negative deflection in the spike waveform were extracted. The probability distributions of the spike times around the stimulation (2 s before to 3 s after the stimulation) with a binning of 0.1 s were calculated and averaged for each experiment (10–20 trials per animal) and are represented as multi-unit probability (MU Probability).

5. Voltage sensitive dye (VSD) imaging

5.1. Surgery

Six month-old YAC128 Line 53 on an FVB background and wild-type FVB mice underwent an craniotomy. Mice were anesthetized with isoflurane at 3–5% for induction and maintained at 1.0–1.5% during imaging. Mice were placed on a metal plate that could be mounted on the stage of an upright microscope and the skull was fastened to a steel plate. A 7 × 6 mm unilateral craniotomy (bregma 2.5 to – 4.5 mm, lateral 0 to 6 mm) was made and underlying dura removed as described previously (Mohajerani et al., 2010; Mohajerani et al., 2013). Body temperature was maintained at 37 °C with a heating pad and feedback thermistor.

5.2. VSD imaging

VSD imaging was performed as described previously (Mohajerani et al., 2010; Mohajerani et al., 2013). Briefly, the dye RH1692 (Optical Imaging, New York, NY) was dissolved in HEPES-buffered saline solution (1 mg ml−1) and applied to the exposed cortex for 60–90 min for each mouse, staining neocortical layers. VSD imaging began ~30 min following washing unbound VSD. The brain was covered with 1.5% agarose made in HEPES-buffered saline to minimize movement artifacts, and sealed with a glass coverslip. 12-bit images were captured at 150 Hz with a CCD camera (1 M60 Pantera, Dalsa, Waterloo, ON) and EPIX E4DB frame grabber with XCAP 3.8 imaging (EPIX, Inc., Buffalo Grove,
IL). The VSD was excited using a red LED (Luxeon K2, 627 nm) with excitation filters 630 ± 15 nm. Images were recorded through a macroscope composed of front-to-front video lenses (8.6 × 8.6 mm field of view, 67 μm pixel−1) with 1 mm depth of field. Fluorescence was filtered using a 673–703 nm bandpass optical filter (Semrock, New York, NY). For limb stimulation experiments, 10–45 trials of stimulus presentation were averaged to reduce the effects of on-going spontaneous activity. There was a 10 s interval between stimulation trials, and non-stimulation trials were collected and used for normalization of stimulated data.

5.3. Analysis

All VSD responses were expressed as percentage relative to baseline VSD responses (F0−Ft/F0)*100, where F0 is the baseline at the start of the trial, to reduce regional biases in VSD signal caused by uneven loading of the dye (calculated using MATLAB).

For region-based analyses, the coordinates of the hindlimb primary sensory area were determined by centering a 5 × 5 pixel ROI over the initial point of response to contralateral hindlimb stimulation for each animal. Similarly, forelimb sensory areas and barrel cortex sensory areas were experimentally mapped. The coordinates for other brain areas of interest were determined based on relative position to the hindlimb primary sensory area and stereotaxic coordinates as described previously (Mohajerani et al., 2013; Afrashteh et al., 2017).

Sensory stimulations typically initiated waves of VSDI-measured activity which spread from modality appropriate sensory areas across the cortical surface. We first employed a threshold approach in Fiji-ImageJ to compare the extent of this sensory-mediated activity spread between genotypes. To do so, the exposed cortical surface in each ΔF/F VSDI movie was manually traced and the whole cortex area stored as a region of interest (ROI). The root mean square (RMS) noise of ΔF/F magnitude at each pixel within the ROI was measured during the initial 200 ms (baseline) of a movie prior to sensory stimulation. The peak ΔF/F value following sensory stimulation was identified at each pixel with a maximum signal projection of the entire movie and this value divided by a given pixel’s baseline RMS noise. The cortical area activated following sensory stimulations was determined by pixels active over a 5 × baseline RMS noise threshold and compared between animals (Similar genotype differences were seen when this threshold was varied between 3–10 × RMS noise).

Notably, the cortical area activated following sensory stimulation increased with stimulation intensity, but in the cases of forelimb and hindlimb stimulations typically plateaued at 0.5–1.0 mA intensities. This maximum (plateau) value was specifically examined to facilitate signal spread, it could be biased by differences in baseline RMS noise between animals and only examined each pixel’s maximum ΔF/F value following stimulation. Therefore, we also examined, and compared between genotypes, spatially averaged ΔF/F time-courses at select 5 × 5 pixel ROIs (outlined above) during plateau amplitude sensory stimulations.

5.4. Optical flow analysis

Optical Flow analysis of the VSD data was performed using MATLAB and Graphpad Prism. The Optical-Flow Analysis Toolbox (OFAMM) for MATLAB (http://lathbridgebraindynamics.com/ofamm/) was used to analyze the spatiotemporal dynamics of the VSD data (Mohajerani et al., 2010). This toolbox allows us to estimate the spatiotemporal dynamics, such as trajectory and speed, of pixels in our VSD recordings, using a variety of optical flow analysis methods. We used the Horn-Schuck (HS) method (Afrashteh et al., 2017; Horn and Schunck, 1981) for our optical flow analysis, and repeated select analyses with the Combined Local-Global (CLG) method, which combines the HS method with the Lucas-Kanade (LK) method (Afrashteh et al., 2017; Bruhn et al., 2005; Jara-Wilde et al., 2015). The main difference between these methods is that the LK method assumes a pixel’s motion is constant relative to neighboring pixels, whereas the HS method does not make this assumption (Afrashteh et al., 2017).

Optical flow analysis of 9 × 9 pixel (603 × 603 μm) regions of interest for hindlimb, forelimb, and barrel cortex primary and secondary sensory areas, as well as motor barrel cortex, was performed, to determine the trajectory and temporal speed of activity originating or flowing through that region in response to sensory stimulation. Regions were determined functionally through sensory stimulation or in relation to bregma.

5.5. Whole-cell voltage clamp in acute cortical slice experiments

Mice were anesthetized with isoflurane, decapitated and the brain rapidly removed. Sagittal brain slices (300 μm) with sensory cortex were cut on a vibratome (VT1000 Leica) in ice cold artificial cerebrospinal fluid (aCSF, as below except 0.5 mM CaCl2 and 2.5 mM MgCl2) containing Kynurenic acid (1 mM) and bubbled with 95%O2/5%CO2. Slices were transferred to a holding chamber with aCSF (in mM: 125 NaCl, 2.5 KCl, 1.25 NaH2PO4, 2 CaCl2, 1 MgCl2, 25 NaHCO3, 10 glucose with osmolality 310 mOsm) at 37 °C for 40 min then kept at room temperature. Layer 2/3 pyramidal neurons were selected on their shape and apical dendrites. For recording evoked excitatory postsynaptic currents (EPSCs) pipettes (resistance 3–5MΩ) were filled with intracellular recording solution containing (in mM: 130 CsMe, 5 CsCl, 4 NaCl, 1 MgCl2, 10 HEPES, 5 EGTA, 5 QX314Cl, 1 NaGTP, 10 Na-phosphocreatine, 1 MgATP at pH 7.3 and 290 mOsm). Stimulation was through a glass micropipette filled with aCSF positioned >300 μm ventral to the neuron. Neurons were recorded at +30 mV in aCSF with added GABA A receptor antagonist 50 μM Picrotoxin (PTX) and 10 μM AMPA/kainate receptor antagonist 6-cyano-2,3-dihydroxy-7-nitro-quinoxaline (CNQX). A stimulation train of 10 × 0.1 ms at 20 Hz was delivered every 30 s and recorded for >5 min. The GLT1/EAA2 blocker DL-threo-b-Benzyloxyaspartic acid (TBOA, 30 μM) was bath-applied for 15 min. The recording solution for spontaneous inhibitory postsynaptic currents (IPSCs) in layer 2/3 was as above with BAPTA in the internal solution and recordings were made without any drugs in the bath and neurons were held at +10 mV. Neurons in layer 5 sensory cortex were held at -70 mV with TTX and CNQX in the bath and using a high Cl internal solution containing (in mM: 130 CsCl, 5 NaCl, 10 HEPES, 0.5 EGTA, 4 MgATP, 0.3 Na2GTP, 5 QX-314Cl) to record miniature IPSCs.

5.6. Statistics

Statistical analysis was calculated with GraphPad Prism. LFP power was compared by 2-way ANOVA of area under the curve of normalized power for 1.5 s following stimulus and Siddik’s multiple comparisons test (Figs. 1, 2, 5 and 6). Unpaired, two-tailed Student’s t-test was used to compare the VSDI area activated with hindlimb stimulation (Fig. 3B), layer 5 mIPSC frequency and amplitude (results text), layer 2/3 membrane properties, sIPSC frequency, and amplitude (results text and Fig. 4B) and isoflurane burst suppression (Supplemental Fig. 1B,C,E and F). Number of cells with NMDAR events were compared by Chi-square (Fig. 4A) and TBOA effects on frequency and amplitude by Kruskal-Wallis ANOVA with Dunn’s multiple comparisons post hoc (Fig. 4E). P values less than 0.05 were considered significant. In whole-cell voltage clamp experiments n indicates the number of cells with the number of animals shown in brackets. For all other experiments n = number of animals. The distributions for VSDI trajectory length and maximum temporal speed (determined by optical flow analysis) were compared using the two-sample Kolmogorov-Smirnov test (Fig. 3C and Supplemental Fig. 4).
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Appendix A. Supplementary data

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