



REVIEW ARTICLE

Aberrant brain network connectivity in presymptomatic and manifest Huntington's disease: A systematic review

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Abstract

Resting-state functional magnetic resonance imaging (rs-fMRI) has the potential to shed light on the pathophysiological mechanisms of Huntington's disease (HD), paving the way to new therapeutic interventions. A systematic literature review was conducted in three online databases according to PRISMA guidelines, using keywords for HD, functional connectivity, and rs-fMRI. We included studies investigating connectivity in presymptomatic (pre-HD) and manifest HD gene carriers compared to healthy controls, implementing seed-based connectivity, independent component analysis, regional property, and graph analysis approaches. Visual network showed reduced connectivity in manifest HD, while network/areas underpinning motor functions were consistently altered in both manifest HD and pre-HD, showing disease stage-dependent changes. Cognitive networks underlying executive and attentional functions showed divergent anterior-posterior alterations, possibly reflecting compensatory mechanisms. The involvement of these networks in pre-HD is still unclear. In conclusion, aberrant connectivity of the sensory-motor network is observed in the early stage of HD while, as pathology spreads, other networks might be affected, such as the visual and executive/attentional networks. Moreover, sensory-motor and executive networks exhibit hyper- and hypo-connectivity patterns following different spatiotemporal trajectories. These findings could potentially help to implement future huntingtin-lowering interventions.

KEYWORDS

functional connectivity, Huntington's disease, resting state networks, systematic review

1 | INTRODUCTION

Resting-state functional magnetic resonance imaging (rs-fMRI) investigates spontaneous fluctuations of blood oxygenation level dependent

Abbreviations: ALFF, amplitude of low frequency fluctuations; DAN, dorsal attention network; DMN, default mode network; ECN, executive network; FPN, frontoparietal network; HC, healthy controls; HD, Huntington's disease; ICA, independent component analysis; Pre-HD, presymptomatic Huntington's disease; ReHo, regional homogeneity; rs-fMRI, resting state functional magnetic resonance imaging; SMN, sensory-motor network; VIS, visual network.

signal, which could serve as a proxy for neural activity (Matsui, Murakami, & Ohki, 2016; Schwalm et al., 2017). Cortical and subcortical anatomically separated brain regions which exhibit low frequency (0.01–0.1 Hz) blood oxygen fluctuations correlated in time are assumed to be functionally connected into resting state networks, linked with specific cognitive and motor functions (Damoiseaux et al., 2006). This methodology is emerging as a promising tool to identify brain functional alterations in neurodegenerative pathologies such as Huntington's disease (HD), and might help to better understand early

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pathophysiological mechanisms and to assess the effectiveness of HD clinical trials (Bohanna, Georgiou-Karistianis, Hannan, & Egan, 2008; Ross & Tabrizi, 2011).

HD is a progressive neurodegenerative genetic disease caused by CAG repeat expansion in the huntingtin (*HTT*) gene, encoding for an abnormal conformation of mutant *HTT* protein (Ross & Tabrizi, 2011). This mutation exhibits toxic features and is responsible for pathological brain alterations, leading to progressive functional disability in gene carriers (Ross & Tabrizi, 2011). For individuals in the stage preceding the clinical symptomatology onset (referred to as presymptomatic HD; pre-HD), the disease burden score, that takes into account the number of CAG repeats and mutation gene carrier's age (Penney Jr., Vonsattel, MacDonald, Gusella, & Myers, 1997), estimates the cumulative toxicity of the mutant *HTT*.

The neuroanatomical hallmark of HD includes early loss of GABAergic inhibitory neurons and atrophy of the striatum (Postuma and Dagher, 2006). As pathology proceeds, neuronal degeneration spreads to the cortex and other extrastriatal regions (Nanetti et al., 2018; Rosas et al., 2008). However, the relationship between brain atrophy and clinical symptoms is still unclear.

Emerging findings suggest that functional imaging might identify changes in HD before structural brain damage, accounting for the onset of symptoms (Ross et al., 2014). Specifically, the disruption of resting-state networks identified through rs-fMRI might provide an intermediate phenotype between neuropathology and clinical symptoms. This hypothesis has been largely investigated in several brain disorders. In Alzheimer's disease (AD), the pattern of atrophy mirrors the topography of the default mode network (DMN), whereas frontotemporal dementia displays an atrophy pattern coherent with the layout of the salience network (Seeley et al., 2009). Moreover, in AD functional abnormalities of the DMN have been linked with the molecular hallmark (i.e., beta-amyloid deposition) and memory deficits (Buckner et al., 2005). The salience network, which is involved in detecting and filtering relevant social information (Menon, 2015), shows aberrant connectivity in neurodegenerative and psychiatric disorders sharing deficits in social cognition (Quattrini et al., 2018; Zhou et al., 2010). Preliminary results in Parkinson's disease (PD) seem to point out the involvement of a subcortical network (Guan et al., 2017). Similarly, a strong fit between the source of atrophy and functional connectivity patterns was reported in semantic dementia, progressive nonfluent aphasia and corticobasal syndrome, suggesting a selective vulnerability of specific resting-state networks to different neurodegenerative diseases (Seeley et al., 2009).

The relation between the disruption of neural networks and HD onset and progression is still poorly understood. Recently, Hohenfeld, Werner, and Reetz (2018) reported an extensive review of rs-fMRI findings in several neurodegenerative diseases. Their aim was to investigate whether rs-fMRI can serve as a reliable diagnostic biomarker. They reported connectivity alteration in sensorimotor (SMN), visual (VIS) and subcortical (especially the striatum) networks in HD, although no considerations were reported about the directionality of these alterations. Conversely, the aim of the present review is to examine the brain functional fingerprint within the whole HD spectrum, and the direction of

functional changes compared to healthy controls (i.e., aberrant hyper- or hypo-connectivity). Different functional imaging approaches have been applied to HD to enhance our understanding of the pathophysiology and potential compensatory mechanisms at play. These methods include seed-based connectivity, whole-brain independent component analysis (ICA), regional property measures and graph analysis. This review examines the contribution of these rs-fMRI techniques to identify specific alterations in distinctive functional neural-pathways, and specific mechanisms linked with increased or decreased connectivity (i.e., detrimental or compensatory processes). Results might help to better understand pathophysiological mechanisms of HD, and might be used as targets or surrogate outcomes in new clinical trials.

2 | METHODS

2.1 | Study selection

A systematic literature search of rs-fMRI studies was conducted according to *The PRISMA Statement*, a checklist of items and guidelines to collect, check, and critically appraise data for reporting systematic review and meta-analysis (Liberati et al., 2009). We searched PubMed, EMBASE, and Web of Science databases for rs-fMRI articles using different combinations of keywords (Huntington AND "resting state"; Huntington AND "functional connectivity"; Huntington AND "functional network"). Further studies were identified through tracing of the retrieved articles and relevant reviews. Figure 1 shows the PRISMA flowchart. We included studies published in English investigating rs-fMRI in both pre-HD individuals and manifest HD patients compared to controls or reporting significant relationship between connectivity and genetic load. Aberrant connectivity of large-scale functional networks was inferred from the findings of studies implementing seed-based connectivity, ICA, and network-of-interest

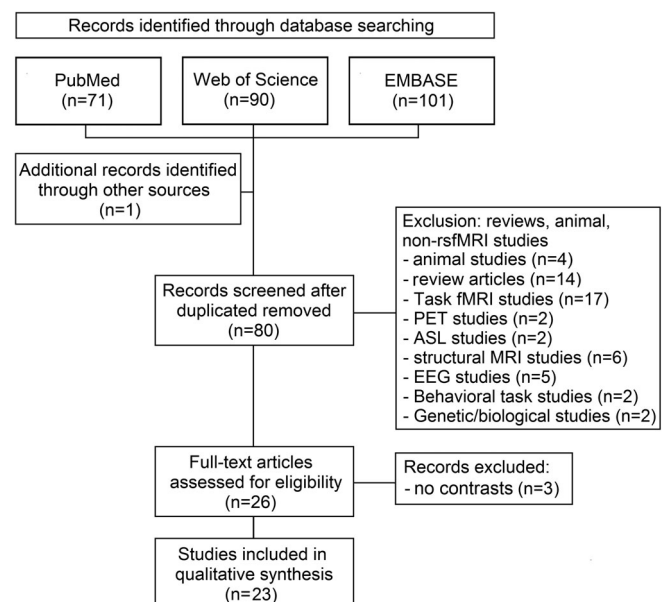


FIGURE 1 PRISMA flow diagram of the literature search

ICA-based methods. Additionally, studies implementing amplitude of low frequency fluctuations (ALFF), regional homogeneity analysis (ReHo), and graph approaches were included to investigate regional abnormalities of key brain regions belonging to different functional networks. Exclusion criteria were: (a) non rs-fMRI studies (e.g., task fMRI, positron emission tomography, electroencephalography studies); (b) reviews and meta-analyses; (c) animal studies; and (d) conference proceedings or abstracts.

2.2 | Data extraction

From the full articles of the eligible studies, the following variables were recorded: population characteristics (sample size, age, gender, education years, mean age disease, unified Huntington's disease rating scale [UHDRS], and mini-mental state examination scores), resting state networks investigated, methods for network analysis, acquisition characteristics (scanner field strength, acquisition time), and correlations with disease burden or CAG repeats and cognitive/motor outcomes. Studies reporting overlapping samples or a subset of rs-fMRI data (Espinoza et al., 2018; Harrington et al., 2015; Koenig et al., 2014; Wolf, Sambataro, Vasic, Baldas, et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014; Wolf et al., 2015) were included.

3 | RESULTS

Database searching identified 263 articles, which yielded 80 citations after duplicates were removed. Fifty-four articles were excluded because reporting analysis in animals ($n = 4$), reviews ($n = 14$), or no rs-fMRI studies (task fMRI, $n = 17$; positron emission tomography, $n = 2$; arterial spin labeling, $n = 2$; structural MRI, $n = 6$; electroencephalography, $n = 5$; behavioral task, $n = 2$; genetic/biological studies $n = 2$). Twenty-six full-text articles were assessed for eligibility. Three of these articles were further excluded because not reporting connectivity contrasts between HD versus healthy controls (HC) or correlation with genetic load. The 23 articles included in the final review encompassed 648 HC (sample range 10–94), 266 manifest HD (sample range 10–34) and 641 pre-HD (sample range 10–183) individuals (Table 1). Table 2 lists the studies reporting aberrant rs-fMRI connectivity in pre-symptomatic Huntington's disease individuals compared to healthy controls, separately for each specific network involved. Twelve articles reported correlations between genetic load (i.e., disease burden score or CAG repeat length) and connectivity (Table 3).

A total of 22 studies reported contrasts between HD and/or pre-HD versus HC, while only 1 study was considered as reporting significant relationship between connectivity and genetic load. The majority of studies comparing HD to controls involved the SMN ($n = 6$) and the VIS ($n = 5$), while the cerebellum and the auditory networks, were investigated only by $n = 3$ and $n = 2$ studies, respectively. The DMN, the executive network (ECN), and the frontoparietal network (FPN) were equally investigated ($n = 4$ studies each network), while $n = 3$ studies investigated the dorsal attention (DAN) and the subcortical

networks. In pre-HD the SMN was the most investigated ($n = 6$ studies). The VIS was reported by $n = 4$ studies, the auditory network by $n = 3$ studies, while the cerebellar network was poorly investigated ($n = 1$ study). The number of studies was similar for the DMN ($n = 4$ studies), the ECN ($n = 3$ studies), and the FPN ($n = 3$ studies), while the DAN was reported by only two studies. The subcortical network was reported by two studies, while a single study investigated the salience network. Finally, $n = 3$ studies and $n = 5$ studies investigated regional functional properties or whole brain graph measures in manifest and pre-HD, respectively.

A total of eight studies implemented seed-based connectivity approaches, three studies used a predefined network of interest approach, and whole brain ICA was performed in six of the included studies. Six studies implemented different metrics, such as graph analysis approaches ($n = 4$), and ALFF ($n = 2$), while one study implemented ReHo analysis.

3.1 | Sensory and motor networks

In manifest HD the VIS showed abnormal functional connectivity changes in 4 out of 5 independent studies (Coppin et al., 2018; Dumas et al., 2013; Werner et al., 2014; Wolf, Sambataro, Vasic, Baldas, et al., 2014). Reduced connectivity within this network was functionally related to lower attention, visual scanning, and motor speed and with higher disease burden scores (Wolf, Sambataro, Vasic, Baldas, et al., 2014). One study (Wolf, Sambataro, Vasic, Baldas, et al., 2014) reported concomitant increased connectivity, according to the study of Werner et al. (2014). However, no correlations were found between higher connectivity and disease burden, or clinical/motor impairment (Werner et al., 2014; Wolf, Sambataro, Vasic, Baldas, et al., 2014). Therefore, VIS hypoconnectivity might account for worse visuomotor cognition in manifest HD patients, while hyperconnectivity is not related to genotype and clinical symptoms of HD. VIS impairment prior to motor symptom onset is less clear. Most of the studies in pre-HD did not report changes within this network compared to HC (Coppin et al., 2018; Odish et al., 2015; Poudel et al., 2014). Only Dumas et al. (2013) showed reduced connectivity in the medial VIS, in brain regions positioned outside the canonical visual mask (i.e., left frontal and right parietal lobules), leaving it unknown whether this connectivity pattern could reflect early changes within the VIS.

The SMN showed consistent functional connectivity alterations in both manifest (Müller et al., 2016; Sánchez-Castañeda et al., 2017; Wolf, Sambataro, Vasic, Depping, et al., 2014; Werner et al., 2014) and pre-HD (Koenig et al., 2014; Poudel et al., 2014; Unschuld et al., 2012). Specifically, in manifest HD several studies reported aberrant SMN increased connectivity, which correlated with worse motor functions (Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014) and impaired cognitive abilities (Sánchez-Castañeda et al., 2017). Congruently, the cerebellum, a brain region structurally and functionally linked with motor and cognitive functions (Chen & Desmond, 2005; Laird et al., 2011; Nitschke, Arp, Stavrou, Erdmann, & Heide, 2005), showed aberrant increased connectivity (Werner et al.,

TABLE 1 Rs-fMRI studies reporting aberrant rs-fMRI connectivity in manifest Huntington's disease patients compared to healthy controls

Reference	Huntington's disease patients			Healthy controls			Main findings	Analysis
	Sample (% F)	Age (y ± SD)	Education (y ± SD)	Sample (% F)	Age (y ± SD)	Education (y ± SD)		
<i>Visual network</i>								
Wolf, Sambataro, Vasic, Baldas, et al., 2014	20 (30%)	49 ± 9	13 ± 2	20 (35%)	47 ± 9	14 ± 2	Both decreased and increased FC	ICA
Coppen, Grond, Hafkemeijer, Barkey Wolf, & Roos, 2018	20 (45%)	52 ± 11	16 ± 2	18 (61%)	46 ± 11	17 ± 2	Decreased FC	Network of interest
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	Decreased FC	Network of interest
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Increased FC	ICA
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
<i>Sensory-motor network</i>								
Wolf, Sambataro, Vasic, Depping, et al., 2014	20 (30%)	49 ± 9	13 ± 2	20 (35%)	47 ± 9	14 ± 2	Increased FC	ICA
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Increased FC	ICA
Sánchez-Castañeda et al., 2017	10 (40%)	39 ± 19	Na	10 (40%)	38 ± 16	Na	Increased FC	Seed
Müller et al., 2016	34 (29%)	47 (32–65)	13 (9–20)	32 (38%)	48 (25–62)	14 (11–19)	Decreased FC	Seed
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	No differences	Network of interest
<i>Cerebellum network</i>								
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Increased FC	ICA
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
Wolf et al., 2015	20 (30%)	49 ± 9	13 ± 2	20 (35%)	47 ± 9	14 ± 2	No differences	Seed
<i>Auditory network</i>								
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	No differences	Network of interest
<i>Executive network</i>								
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Frontal increased FC	ICA
Wolf, Sambataro, Vasic, Depping, et al., 2014	20 (30%)	49 ± 9	13 ± 2	20 (35%)	47 ± 9	14 ± 2	Posterior decreased FC; anterior increased FC	ICA
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	Posterior/subcortical decreased FC	ICA
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	Posterior/subcortical decreased FC	Network of interest
<i>Frontoparietal network</i>								
Wolf, Sambataro, Vasic, Depping, et al., 2014	20 (30%)	49 ± 9	13 ± 2	20 (35%)	47 ± 9	14 ± 2	Both decreased and increased FC	ICA
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Increased FC	ICA
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	Increased FC ^c	ICA
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	No differences	Network of interest

(Continues)

TABLE 1 (Continued)

Reference	Huntington's disease patients			Healthy controls			Main findings	Analysis
	Sample (% F)	Age (y ± SD)	Education (y ± SD)	Sample (% F)	Age (y ± SD)	Education (y ± SD)		
<i>Dorsal attention network</i>								
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	Decreased FC	ICA
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Increased FC	ICA
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	No differences	Network of interest
<i>Default mode network</i>								
Quarantelli et al., 2013	26 (38%)	44 ± 12	Na	22 (50%)	39 ± 14	Na	Both decreased and increased FC	Seed
Dumas et al., 2013	20 (75%)	47 ± 11	1–5 ^b	28 (54%)	49 ± 9	2–5 ^b	Decreased FC	Network of interest
Sánchez-Castañeda et al., 2017	10 (40%)	39 ± 19	Na	10 (40%)	38 ± 16	Na	Increased FC	Seed
Poudel et al., 2014	23 (43%)	56 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
<i>Subcortical network</i>								
Wolf, Sambataro, Vasic, Depping, et al., 2014	20 (30%)	49 ± 9	13 ± 2	20 (35%)	47 ± 9	14 ± 2	Both decreased and increased FC	ICA
Werner et al., 2014	17 (59%)	45 ± 10	3 ± 1 ^b	19 (58%) ^a	48 ± 10	4 ± 1 ^b	Increased FC	ICA
Müller et al., 2016	34 (29%)	47 (32–65)	13 (9–20)	32 (38%)	48 (25–62)	14 (11–19)	Decreased FC	Seed
<i>Regional properties and graph measures</i>								
Gargouri et al., 2016	18 (Na %)	51 ± 7	Na	18 (50%)	44 ± 10	Na	Widespread changes in sensorimotor, associative And limbic networks	Graph measures
Liu et al., 2016	10 (90%)	45 ± 9	10 ± 3	20 (90%)	45 ± 8	Na	Decreased PCC/parietal and increased temporo-frontal ALFF	ALFF
Sarappa et al., 2017	28 (39%)	42 ± 10	Na	40 (55%)	37 ± 14	Na	Decreased parietal and increased cerebellum ALFF	ALFF
Sarappa et al., 2017	28 (39%)	42 ± 10	Na	40 (55%)	37 ± 14	Na	Decreased cerebellum and increased frontotemporal ReHo	ReHo

Abbreviations: ALFF, amplitude of low frequency fluctuations; F, female; FC, functional connectivity; Na, not available; PCC, posterior cingulate cortex; ReHo, regional homogeneity; SD; standard deviation; Y, years.

^aThree HD mutation carriers were presymptomatic.

^bInternational Standard Classification of Education.

^cCompared to presymptomatic Huntington's disease individuals.

2014) in manifest HD. On the opposite, Müller et al. (2016) reported reduced SMN connectivity in a sample of 34 manifest HD, which correlated with worse motor abilities. Several factors may account for these contrasting results, such as methodologies (e.g., ICA vs. seed-based connectivity) that might be differently sensible to head motion, a factor known to have systematically different effects on functional connectivity, particularly within the SMN (Van Dijk, Sabuncu, & Buckner, 2012). Alternatively, different disease stages may be related to

divergent changes in SMN connectivity. Indeed, the cohort of Müller et al. (2016) featured a lower impairment of motor abilities (as assessed with motor UHDRS scale). This assumption seems supported by studies in pre-HD individuals, reporting reduced functional connectivity within the SMN (Koenig et al., 2014; Poudel et al., 2014; Unschuld et al., 2012). Lower connectivity in these individuals was associated with worse motor (Poudel et al., 2014) and cognitive abilities (Koenig et al., 2014). Moreover, divergent connectivity

TABLE 2 Rs-fMRI studies reporting aberrant rs-fMRI connectivity in presymptomatic Huntington's disease individuals compared to healthy controls

Reference	Presymptomatic Huntington's disease			Healthy controls			Main findings	Analysis
	Sample (% F)	Age (y ± SD)	Education (y ± SD)	Sample (% F)	Age (y ± SD)	Education (y ± SD)		
<i>Visual network</i>								
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
Odish et al., 2015	22 (55%)	43 ± 9	4 ± 3 ^a	18 (61%)	47 ± 7	4 ± 3 ^a	No differences	ICA
Coppen et al., 2018	21 (48%)	37 ± 9	17 ± 3	18 (61%)	46 ± 11	17 ± 2	No differences	Network of interest
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	Decreased FC	Network of interest
<i>Sensory-motor network</i>								
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	Decreased FC	ICA
Unschuld et al., 2012	10 (40%)	44 ± 9	Na	10 (60%)	42 ± 11	Na	Decreased FC	Seed
Koenig et al., 2014	Low 16 (94%)	33 ± 9	14 ± 2	16 (75%)	43 ± 9	16 ± 2	Increased FC	Seed
	Medium 16 (69%)	40 ± 10	15 ± 3				No differences	
	High 16 (88%)	48 ± 13	14 ± 2				Decreased FC	
Odish et al., 2015	22 (55%)	43 ± 9	4 ± 3 ^a	18 (61%)	47 ± 7	4 ± 3 ^a	No differences	ICA
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	No differences	Network of interest
Gorges et al., 2017	12 (75%)	36 (27–62)	14 (9–17)	22 (32%)	45 (25–51)	17 (12–19)	No differences	Seed
<i>Cerebellum network</i>								
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
<i>Auditory network</i>								
Odish et al., 2015	22 (55%)	43 ± 9	4 ± 3 ^a	18 (61%)	47 ± 7	4 ± 3 ^a	No differences	ICA
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	No differences	Network of interest
<i>Executive network</i>								
Odish et al., 2015	22 (55%)	43 ± 9	4 ± 3 ^a	18 (61%)	47 ± 7	4 ± 3 ^a	No differences	ICA
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	No differences	Network of interest
<i>Frontoparietal network</i>								
Odish et al., 2015	22 (55%)	43 ± 9	4 ± 3 ^a	18 (61%)	47 ± 7	4 ± 3 ^a	No differences	ICA
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	No differences	Network of interest
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA
<i>Dorsal attention network</i>								
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	No differences	Network of interest
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	Decreased FC	ICA
<i>Default mode network</i>								
Dumas et al., 2013	28 (61%)	43 ± 8	2–5 ^a	28 (54%)	49 ± 9	2–5 ^a	No differences	Network of interest
Odish et al., 2015	22 (55%)	43 ± 9	4 ± 3 ^a	18 (61%)	47 ± 7	4 ± 3 ^a	No differences	ICA
Poudel et al., 2014	25 (64%)	43 ± 9	Na	18 (78%)	46 ± 14	Na	No differences	ICA

(Continues)

TABLE 2 (Continued)

Reference	Presymptomatic Huntington's disease			Healthy controls			Main findings	Analysis
	Sample (% F)	Age (y ± SD)	Education (y ± SD)	Sample (% F)	Age (y ± SD)	Education (y ± SD)		
Seibert et al., 2012	34 (59%)	41 ± 10	Na	22 (68%)	40 ± 12	Na	No differences	Seed
<i>Saliency network</i>								
Mason et al., 2018	19 (Na)	46 ± 12	Na	21 (Na)	42 ± 12	Na	Reduced coupling activity mainly between SN and other sensory and cognitive networks	Network of interest
<i>Subcortical network</i>								
Gorges et al., 2017	12 (75%)	36 (27–62)	14 (9–17)	22 (32%)	45 (25–51)	17 (12–19)	No differences	Seed
Seibert et al., 2012	34 (59%)	41 ± 10	Na	22 (68%)	40 ± 12	Na	No differences	Seed
<i>Regional properties and graph measures</i>								
Gargouri et al., 2016	24 (Na)	39 ± 9	Na	18 (50%)	44 ± 10	Na	Decreasing hub organization in associative and SMN networks	Graph measures
Harrington et al., 2015	Low 16 (94%)	33 ± 9	14 ± 2	16 (75%)	43 ± 9	16 ± 2	No differences	Graph measures
	Medium 16 (69%)	39 ± 10	15 ± 3				Weakened connections within ventral attention centers and frontal areas	
	High 16 (88%)	47 ± 13	14 ± 2				Weakened connections within frontostriatal network and stronger in ventral attention and parietal areas	
McColgan, Gregory, et al., 2017	64 (45%)	44 ± 8	Na	66 (67%)	46 ± 8	Na	Increase connectivity in anterior/frontal and decreased in posterior	Graph measures
McColgan, Razi, et al., 2017	92 (47%)	42 ± 10	Na	94 (60%)	48 ± 11	Na	Greater connectivity within parietal-DMN regions	Graph measures
Sarappa et al., 2017	11 (55%)	38 ± 7	Na	40 (55%)	37 ± 14	Na	Decreased precuneus ALFF	ALFF
Sarappa et al., 2017	11 (55%)	38 ± 7	Na	40 (55%)	37 ± 14	Na	Decreased cerebellum and subcortical and increased frontotemporal ReHo	ReHo

Abbreviations: ALFF, amplitude of low frequency fluctuations; F, female; FC, functional connectivity; Na, not available; PCC, posterior cingulate cortex; ReHo, regional homogeneity; SD, standard deviation; Y, years.

^aInternational Standard Classification of Education.

TABLE 3 Rs-fMRI studies investigating correlation between functional connectivity and genetic burden in manifest and presymptomatic Huntington's disease individuals

Reference	Huntington's disease			Healthy controls		Main findings	Analysis
	Sample (% F)	Age (y ± SD)	Disease burden score	Sample (% F)	Age (y ± SD)		
<i>Symptomatic Huntington</i>							
Poudel et al., 2014	23 (43%)	56 ± 9	390 ± 65	18 (78%)	46 ± 14	Higher FPN FC correlated with higher disease burden	ICA
Wolf, Sambataro, Vasic, Baldas, et al., 2014	20 (30%)	49 ± 9	375 ± 69	20 (35%)	47 ± 9	Lower VIS FC correlated with higher disease burden	ICA
Wolf, Sambataro, Vasic, Depping, et al., 2014	20 (30%)	49 ± 9	375 ± 69	20 (35%)	47 ± 9	Lower ECN FC correlated with higher disease burden	ICA
Werner et al., 2014	19 (58%)	48 ± 10	377 ± 79	17 (59%)	45 ± 10	No correlations	ICA
Wolf et al., 2015	20 (30%)	49 ± 9	375 ± 69	20 (35%)	47 ± 9	Lower cerebellar network FC correlated with higher disease burden	Seed
Sánchez-Castañeda et al., 2017	10 (40%)	39 ± 19	51 ± 9 ^a	10 (40%)	38 ± 16	Lower PCC-DMN nodal degree correlated with higher number of CAG repeats	Graph measures
Gargouri et al., 2016	18 (Na %)	51 ± 7	345 ± 83	18 (50%)	44 ± 10	No correlations	Graph measures
<i>Presymptomatic Huntington</i>							
Poudel et al., 2014	25 (64%)	43 ± 9	288 ± 62	18 (78%)	46 ± 14	No correlations	ICA
Espinoza et al., 2018	183 (71%)	42 ± 13	42 ± 3 ^a	78 (68%)	49 ± 11	Lower subcortical FC correlated with higher number of CAG repeats	ICA
Odish et al., 2015	22 (55%)	43 ± 9	43 ± 3 ^a	18 (61%)	47 ± 7	No correlations	Network of interest
Mason et al., 2018	19 (Na)	46 ± 12	275 ± 49	21 (Na)	42 ± 12	Negative correlation between overall hypoconnectivity and disease burden	Network of interest
Koenig et al., 2014	16 (88%)	47 ± 13	439 ± 46	16 (75%)	43 ± 9	Lower SMN FC was associated with higher disease burden	Seed
Gargouri et al., 2016	24 (Na %)	39 ± 9	303 ± 40	18 (50%)	44 ± 10	Correlation between burden score and graph measures in the SMN	Graph measures
Harrington et al., 2015	48 (83%)	40 ± 10	341 ± 1	16 (75%)	43 ± 9	Strengthened whole-brain FC of the inferior parietal lobe correlated with higher disease burden	Graph measures

DMN, default mode network; ECN, executive network; FC, functional connectivity; SMN, sensory-motor network; VIS, visual network, FPN, frontoparietal network.

^aStudies reporting CAG repeat length.

changes in SMN were also observed between pre-HD with lower and higher 5-year probability of a clinical diagnosis (Koenig et al., 2014), which may suggest divergent connectivity abnormalities according to disease stage. Therefore, increased connectivity within the “motor corticocerebellar system” may characterize the manifest HD stage and linked with characteristic motor symptoms, while in the prodromal stage reduced “motor system” connectivity is observed.

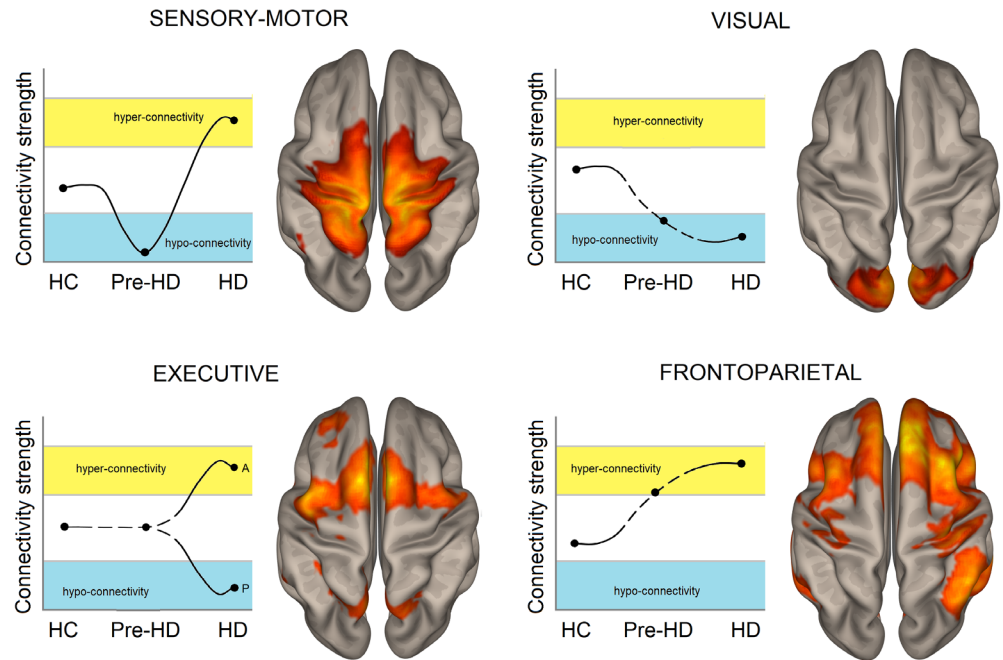
Correlations between functional connectivity and disease burden confirmed the involvement of VIS and cortical-cerebellar motor networks in the whole HD spectrum (Espinoza et al., 2018; Koenig et al., 2014; Wolf, Sambataro, Vasic, Baldas, et al., 2014; Wolf et al., 2015).

The auditory network did not show selective vulnerability at rest in either manifest or pre-HD (Dumas et al., 2013; Odish et al., 2015; Poudel et al., 2014).

3.2 | Executive, frontoparietal, and attentional networks

Several studies investigated functional connectivity within neural networks subserving cognitive domains, such as the ECN, which showed both reduced (Dumas et al., 2013; Poudel et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014) and increased connectivity (Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014) in

FIGURE 2 Pattern of aberrant connectivity in the sensory-motor and visual networks (top row) and executive and frontoparietal networks (bottom row) in the clinical Huntington disease (HD) spectrum. Dashed lines: unclear pattern of connectivity based on preliminary results from literature for presymptomatic HD. A, anterior/frontal regions; HC, healthy controls; P, posterior/parietal regions; pre-HD, presymptomatic HD [Color figure can be viewed at wileyonlinelibrary.com]



manifest HD. This divergent pattern (i.e., hypo- vs. hyper-connectivity) seems to follow different spatial trajectories: decreased connectivity mapped mainly to parietal cortex and subcortical structures (Dumas et al., 2013; Poudel et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014); increased connectivity involved instead the frontal cortex (Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014). Posterior ECN connectivity decrease was related with impaired cognitive abilities and higher disease burden (Wolf, Sambataro, Vasic, Depping, et al., 2014). Conversely, no associations were found for anterior hyperconnectivity (Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014), suggesting that only posterior down-regulation might be linked with phenotype and genotype of HD. However, studies investigating changes in connectivity within the ECN in pre-HD implementing ICA approaches failed to report abnormalities (Dumas et al., 2013; Odish et al., 2015; Poudel et al., 2014).

Increased FPN connectivity was reported in manifest HD and was related to motor and clinical deficits (Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014). Similarly, increased synchronization in the right hippocampus and left dorsolateral prefrontal clusters of FPN was reported in manifest HD compared to the presymptomatic phase of the disease, showing positive correlation with disease burden score (Poudel et al., 2014). However, in pre-HD individuals several studies failed to report changes in FPN (Dumas et al., 2013; Odish et al., 2015; Poudel et al., 2014), leaving the question related to its involvement in early HD stage still unsettled.

Findings within the DAN did not allow to reach univocal interpretations. Preliminary results showed reduced connectivity in pre-HD and manifest HD, despite this pattern mapped in different cortical regions in the two groups (Poudel et al., 2014). Conversely, Dumas and co-workers (2013) did not observe neural synchrony changes in the whole clinical spectrum of HD, whereas only one study reported increased connectivity in manifest HD (Werner et al., 2014).

3.3 | Default mode and salience networks

In manifest HD, DMN-key brain regions (i.e., ventromedial prefrontal cortex and angular gyrus) showed reduced functional connectivity (Dumas et al., 2013; Quarantelli et al., 2013). However, increased connectivity was also observed in these patients (Quarantelli et al., 2013; Sánchez-Castañeda et al., 2017), although only reduction of DMN-hubs was associated with both genotype and cognitive performance (Quarantelli et al., 2013). Studies investigating DMN in pre-HD through ICA or seed-based connectivity approaches did not report connectivity changes (Dumas et al., 2013; Odish et al., 2015; Poudel et al., 2014; Seibert, Majid, Aron, Corey-Bloom, & Brewer, 2012), leaving open the question about the DMN involvement in the early stage of HD.

To date, no study assessed connectivity changes within the salience network. However, two different studies, investigating long range coupling activity between functional networks in pre-HD, showed reduced connectivity between salience network and several networks. Espinoza et al. (2018) reported reduced connectivity between insula and subcortical structures related with increasing CAG repeat length. Similarly, Mason and associates (2018) revealed that in pre-HD participants the majority of the significant hypoconnectivity connections included the salience network.

3.4 | Subcortical network

From the literature, we retrieved only three studies investigating connectivity within the subcortical network in manifest HD (Müller et al., 2016; Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014), reporting contrasting results. Müller et al. (2016) reported reduced basal ganglia-thalamic connectivity, whereas Werner and co-workers (2014) showed increased connectivity in thalamus, caudate and putamen network. A third independent study reported decreased

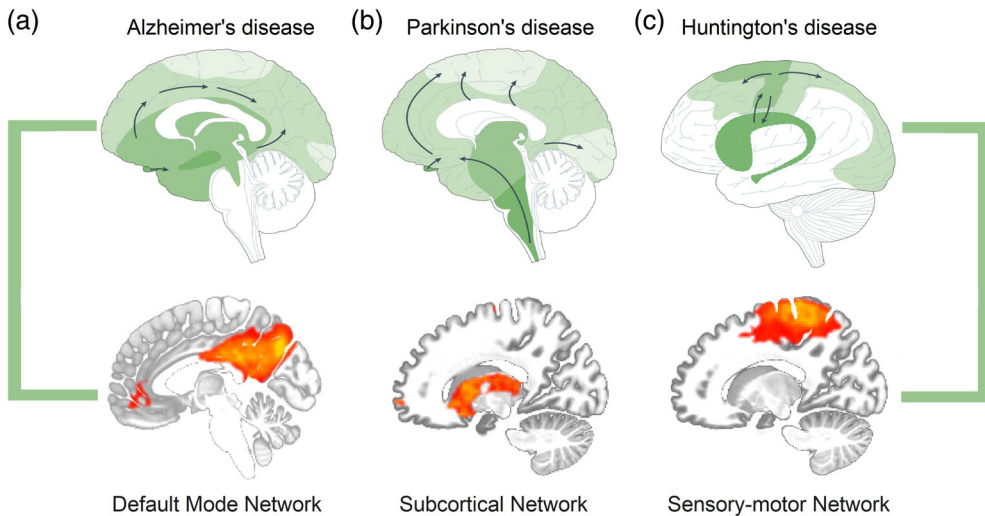


FIGURE 3 Progression of neuropathological changes in Alzheimer's, Parkinson's, and Huntington's disease (top row) overlapping with specific neural networks (bottom row). Functional connectivity maps were extracted through independent component analysis from a sample of 22 healthy individuals. Figure is adapted from Brundin, Melki, and Kopito (2010) with permission from Springer Nature [Color figure can be viewed at wileyonlinelibrary.com]

connectivity in thalamus and temporal gyrus of subcortical network, whereas increased connectivity was observed within the frontal gyrus (Wolf, Sambataro, Vasic, Depping, et al., 2014). In pre-HD, two independent studies, implementing a seed-based connectivity approach, failed to report network changes (Gorges et al., 2017; Seibert et al., 2012).

3.5 | Regional spontaneous brain activity and graph measures

Studies investigating regional spontaneous brain activity (i.e., ALFF and ReHo) and graph measures corroborated the findings about the involvement of the cortical-cerebellar motor circuit in both pre-HD and HD. Sarappa et al. (2017) reported reduced cerebellar ReHo in both HD and pre-HD, while Gargouri and co-workers (2016) found a progressive disruption in brain topology within the SMN, which becomes more randomly connected as the clinical diagnosis of HD approaches.

Interestingly, as reported by studies investigating functional connectivity within the ECN, graph measures showed a similar antero-posterior dissociation in pre-HD: stronger connections (i.e., upregulation) were reported in anterior/frontal regions, whereas weaker connections (i.e., downregulation) were reported in posterior/parietal brain regions (McColgan, Gregory, et al., 2017). Similarly, a divergent connectivity pattern was reported in pre-HD individuals stratified according to CAG-age product (Harrington et al., 2015), a proxy variable for time to diagnosis accounting for the cumulative toxicity of exposure to the CAG expansion (Paulsen et al., 2014). Pre-HD subjects with lower toxicity exposure to CAG reported no connectivity differences, while medium-toxicity pre-HD showed weakened posterior-anterior connections (Harrington et al., 2015). Subjects with higher-toxicity (i.e., with the highest odds for a clinical diagnosis of HD), reported the greatest number of weakened connections within brain areas roughly corresponding to the ECN, while increased connectivity was observed between ventral posterior, frontal and subcortical regions (Harrington et al., 2015).

Finally, these measures captured functional alterations in brain regions overlapping with the posterior key areas of the DMN in both HD patients and pre-HD individuals (Liu et al., 2016; McColgan, Razi,

et al., 2017), suggesting that regional and graph measures might be more accurate to identify changes within this network.

4 | DISCUSSION

The core results of this review are: (a) multiple resting state networks subserving sensory-motor abilities and cognitive functions are involved in the pathophysiological mechanisms of HD, which could be involved in the triad of symptoms (motor, cognitive and psychiatric) of this pathology; (b) the SMN and the ECN exhibited a divergent spatiotemporal connectivity pattern. Specifically, SMN showed a temporal divergent pattern (pre-HD vs. HD), while for the ECN was reported a spatial divergence (posterior vs. anterior). These findings could shed light into the spatiotemporal spreading of brain alteration in HD, revealing detrimental and compensatory mechanisms that could drive new interventions.

4.1 | Functional networks involved in HD

The VIS showed reduced connectivity in manifest HD, which can account for the worse visuomotor performance in HD patients (Say et al., 2011), although its involvement in the prodromal stage of disease is less clear (Figure 2). A main involvement of SMN was reported in both pre-HD and manifest HD suggesting early connectivity changes of this network (Figure 2), consistent with reports in the literature on impairment of motor functions (Ross et al., 2014).

Regarding networks subserving cognitive functions, the ECN showed consistent alterations in manifest HD patients (Figure 2), which might be linked with working memory deficits, one aspect of cognition often impaired in HD (Dumas et al., 2012; Possin et al., 2017; You et al., 2014). Conversely, in pre-HD individuals, the ECN showed no connectivity changes. The involvement of other networks such as the DAN and the subcortical network is less clear, due to the limited literature and the contrasting results. Even though HD is characterized by subcortical structures dysfunction (Tabrizi et al., 2009), further studies are needed to better clarify the involvement of subcortical changes in connectivity, which may precede subcortical atrophy.

Similarly, further studies are needed to understand the involvement of DMN in the physiopathology of HD. In pre-HD, DMN involvement is even less clear. However, preliminary results in the latter group suggest a divergent connectivity pattern between DMN (increase) and salience network (decrease), which has been observed in other neurodegenerative disorders: in AD, the DMN and the salience network show hypo- and hyper-connectivity, respectively, whereas frontotemporal dementia showed the opposite pattern (Zhou et al., 2010). Further studies should investigate whether these alterations are linked with neuropsychiatric symptoms of HD.

4.2 | Divergent connectivity patterns

The main result of this review regards the directionality of connectivity changes within each resting state network (i.e., hyper- or hypo-connectivity) and the association of these changes with the genotype and the clinical phenotype of HD. Interestingly, resting state networks mainly involved in the course of the disease showed divergent connectivity changes (Figure 2).

Specifically, the SMN might follow disease stage-dependent trajectories: reduced connectivity in pre-HD switches to aberrant hyper-connectivity pattern in manifest HD (Figure 2). These nonlinear trajectory changes of connectivity have been reported also in healthy aging as a function of age (Staffaroni et al., 2018) and in the AD continuum. Indeed, mild cognitive impairment (MCI) patients who subsequently converted to AD, displayed longitudinal increased connectivity within the DMN (Serra et al., 2016) while, in full-blown AD dementia, DMN showed consistent functional connectivity reduction (Zhou et al., 2010). This connectivity shift might reflect compensatory functional neural attempts to deal with the emerging motor symptoms. Alternatively, increased connectivity of SMN might represent a maladaptive reorganization of brain functional architecture in HD, as suggested by studies reporting an association between increased SMN connectivity and lower motor performance (Werner et al., 2014; Wolf, Sambataro, Vasic, Depping, et al., 2014). This assumption has been recently reported also in MCI patients, where DMN hyperactivity detrimentally contributes to cognitive impairment (Gardini et al., 2015). To date, only one study investigated longitudinal connectivity changes within several networks, including the SMN, over a period of 3 years, revealing no differences (Odish et al., 2015). However, the low proportion of patients (less than 20% of the sample) converting to manifest HD during the follow-up might account for a lack of results. Future studies should include larger follow-up periods, to confirm SMN connectivity shifting from pre-HD to manifest HD.

A divergent connectivity pattern was also reported within the ECN, in the anterior–posterior axis. In manifest HD, this network showed posterior reduced connectivity, whereas anterior regions displayed aberrant hyperconnectivity (Figure 2). Despite pre-HD did not show ECN changes, when individuals were stratified according to CAG-age product, similar dissociations were observed. The functional posterior–anterior dissociation might suggest functional architecture reorganization within the ECN, where increased connectivity may

represent a compensatory mechanism to counterbalance down-regulation of posterior brain regions as the disease progresses.

This functional shift from posterior to frontal functioning might reflect and emphasize events that have been shown to happen in normal aging (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). For example, the PASA model (posterior–anterior shift in aging) suggests that increase in anterior activity, particularly frontal, offsets decrease in posterior cortical activations associated with aging (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Vallesi, 2011). Thus, the compensation is likely to reflect increasing load on frontal executive functions as a first reaction to the loss of computing power in posterior areas. Accordingly, FPN—anchored to the bilateral dorsolateral prefrontal cortex and commonly recruited for top-down attention processes (Corbetta & Shulman, 2002; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008)—showed increased connectivity (Figure 2), which might be linked with compensatory mechanisms sustaining emerging cognitive deficits in the presymptomatic stage. This assumption is supported by recent task functional studies reporting increased task-related brain activity in pre-HD individuals compared to HC during task performance (Georgiou-Karistianis et al., 2013; Malejko et al., 2014; Scheller et al., 2013), and by rs-fMRI studies showing an association between increased frontal connectivity and more preserved cognitive function (Gregory et al., 2018; Klöppel et al., 2015), suggesting compensatory responses.

4.3 | Neurobiological and clinical considerations

In HD, neurons in different brain regions accumulate abnormal deposits of misfolded protein, a histopathological hallmark shared with other proteinopathies, such as AD and PD (Braak & Del Tredici, 2016; Saudou & Humbert, 2016). Recent findings suggested that pathogenic proteins, such as beta-amyloid/Tau in AD and alpha-synuclein in PD, can spread in a prion-like fashion via selective functionally connected neural networks, triggering specific clinical phenotypes of brain disorders (Brettschneider, Del Tredici, Lee, & Trojanowski, 2015; Jucker & Walker, 2011; Raj, Kuceyeski, & Weiner, 2012). In AD, neurofibrillary tangles first appear in brain regions overlapping with the DMN (Johnson et al., 2016; Pievani, Filippini, van den Heuvel, Cappa, & Frisoni, 2014), whereas in PD, alpha-synuclein distribution underlies dysfunction of basal ganglia circuitry responsible for the development of typical motor symptoms (DeLong, 1990; Double, Reyes, Werry, & Halliday, 2010). These observations lead to the “molecular nexopathy” model, which suggested that specific neural networks might represent candidate substrates for the spread of proteinopathies causing neurodegeneration (Warren et al., 2013). This model could be extended to HD, where SMN could represent the macroscopic network fingerprint involved in the pathophysiological mechanisms early on, since the results of the present review consistently point out to an involvement of this network already in the pre-clinical stage of HD (Figure 3). As the disease progresses, different networks may be affected, such as VIS, FPN, and ECN, accounting for concomitant sensory and cognitive deficits.

Identification of altered brain connectivity will help future huntingtin-lowering interventions to target the most vulnerable brain

regions at the optimal time-window in order to minimize pathological spread and maximize clinical benefits. For instance, noninvasive brain stimulation interventions may benefit from rs-fMRI findings, helping to identify disrupted functional networks linked with pathophysiological processes and clinical phenotypes of several neurodegenerative disorders (Pievani et al., 2017; Pievani, Pini, Cappa, & Frisoni, 2016; Pini et al., 2019). Similarly, in HD, brain stimulation interventions targeting vulnerable neural networks in the early stage of the disease might offer other clinical alternatives to slow down both onset and disease progression. Moreover, connectivity markers might be useful as a surrogate outcome to evaluate the effectiveness of clinical interventions in pre-HD and might pave the way to the development of future personalized preventive treatments.

4.4 | Strengths and limitations

The main strength of this review is that we investigated connectivity changes within large scale resting-state networks, linked, when possible, to disease burden score and to clinical symptoms of HD. This information might shed light on the mechanisms underlying functional change. (i.e., if hyper- and hypo-connectivity is related to compensatory or detrimental processes). To date no effective treatments have been proved to delay disease onset or progression, and classical pharmacological treatments can only provide symptomatic benefit. Identification of reliable biomarkers is currently a research priority, and vulnerable networks linked with early HD pathophysiological processes are optimal candidate which might pave the way to novel therapeutic trials.

Among the limitations, the small number of studies included limited the results, especially regarding cognitive and subcortical networks in HD. This should be taken into account for future meta-analysis aimed to investigate altered hubs within specific neural networks in both manifest and pre-HD. A second limitation is the high heterogeneity across studies. We included studies investigating connectivity changes through different methodology, which could account for different results. These limitations highlight the need for further research in this field.

5 | CONCLUSION

In summary, the SMN showed consistent connectivity changes in the whole HD spectrum, whereas VIS and executive/attentional network alterations emerged during manifest HD and might account for incoming sensory and cognitive deficits. In addition, we observed divergent connectivity patterns in posterior–anterior axis for the ECN in manifest HD, which could reflect compensatory mechanisms, and a disease stage-dependent shifting in SMN connectivity alterations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

All data used for figures were collected according to the Helsinki Declaration and approved by the local ethics committee of the Henri Mondor Hospital, Créteil, France. All participants signed written informed participation consent.

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