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Functional imaging correlates of akinesia in Parkinson's disease: Still open issues

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ABSTRACT

Akinesia is a major manifestation of Parkinson's disease (PD) related to difficulties or failures of willed movement to occur. Akinesia is still poorly understood and is not fully alleviated by standard therapeutic strategies. One reason is that the area of the clinical concept has blurred boundaries referring to confounded motor symptoms. Here, we review neuroimaging studies which, by providing access to finer-grained mechanisms, have the potential to reveal the dysfunctional brain processes that account for akinesia. It comes out that no clear common denominator could be identified across studies that are too heterogeneous with respect to the clinical/theoretical concepts and methods used. Results reveal, however, that various abnormalities within but also outside the motor and dopaminergic pathways might be associated with akinesia in PD patients. Notably, numerous yet poorly reproducible neural correlates were found in different brain regions supporting executive control by means of resting-state or task-based studies. This includes for instance the dorsolateral prefrontal cortex, the inferior frontal cortex, the supplementary motor area, the medial prefrontal cortex, the anterior cingulate cortex or the precuneus. This observation raises the issue of the multidimensional nature of akinesia. Yet, other open issues should be considered conjointly to drive future investigations. Above all, a unified terminology is needed to allow appropriate association of behavioral symptoms with brain mechanisms across studies. We adhere to a use of the term akinesia restricted to dysfunctions of movement initiation, ranging from delayed response to freezing or even total abolition of movement. We also call for targeting more specific neural mechanisms of movement preparation and action triggering with more sophisticated behavioral designs/event-related neurofunctional analyses. More work is needed to provide reliable evidence, but answering these still open issues might open up new prospects, beyond dopaminergic therapy, for managing this disabling symptom.

1. Introduction

The terms akinesia, hypokinesia, and bradykinesia are classically used to describe the wide range of motor dysfunctions characteristic of Parkinson's disease (PD). According to their etymology, akinesia refers to the total absence of movement, hypokinesia to decreased amplitude of movement, and bradykinesia to slowness in movement execution. However, the terminologies have evolved over time and are now inconsistently used in the literature (Schilder et al., 2017). Among these clinical manifestations, akinesia is certainly the most problematic term and the least understood feature of PD (Rodriguez-Oroz et al., 2009). It is particularly disabling, affects a wide range of actions and has no satisfying therapeutic option (Gauntlett-Gilbert and Brown, 1998; Schrag et al., 2000).

At a clinical level, akinesia is often used interchangeably with the terms bradykinesia and hypokinesia (Abdo et al., 2010; Berardelli et al., 2001; Donaldson et al., 2012; Fahn, 2003; Ling et al., 2012; Rodriguez-Oroz et al., 2009; Schilder et al., 2017). Notably, bradykinesia often represents an umbrella term for all these motor symptoms, as encouraged by the UPDRS. However, to establish the link between these

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motor symptoms and the associated pathophysiological mechanisms, it is necessary to refine terminologies so that they refer not only to the symptoms but also to the underlying neural mechanisms. The definition proposed by Hallett and colleagues (e.g., Hallett, 1990), a failure of willed movement to occur, has been successful for addressing this need. This definition clearly states that: (1) akinesia shall not be confounded with bradykinesia -slowness of movement that is ongoing-, (2) akinesia is related to dysfunctions of brain mechanisms that are responsible for movement preparation and initiation, and (3) akinesia is best characterized at a behavioral level by the time needed to initiate a movement. In other words, this definition refers to slowness or failure in movement initiation that can go up to the total abolition of movement (e.g., Jahanshahi et al., 2015b; Krack et al., 1999). It is both an extension of the original greek terminology and a substantial limitation of the common clinical use of the term.

A common belief is that akinesia is mainly a motor deficit related to dopaminergic (DA) depletion (Holtbernd and Eidelberg, 2012). According to the traditional view, the main symptoms of PD are related to dysfunctions of the motor circuit, which links the motor cortices to specific territories within the basal ganglia (BG) nuclei (Alexander and Crutcher, 1990; DeLong, 1990; Jahanshahi et al., 2015a, 2015b). The loss of DA in PD may cause dysfunctions in the balance between the direct pathway (hypoactivation) and the indirect pathway (hyperactivation), resulting in increased subthalamic nucleus and internal globus pallidus activities, and consequent excessive thalamic inhibition. Accordingly, it has long been assumed that the resulting dysfunction of the thalamocortical loop produces akinesia through its action upon motor cortical regions (Escola et al., 2003; Haslinger et al., 2001; Jahanshahi et al., 2015a, 2015b). However, this view fails to explain several clinical and experimental observations, such as the fact that lesions of the motor thalamus do not result in akinesia (Canavan et al., 1989), that globus pallidus lesions do not improve it (Marsden and Obeso, 1994), or that akinesia is not fully alleviated by standard pharmacological treatments using levodopa or DA agonists (Favre et al., 2013; Fox, 2013; Jahanshahi et al., 1992; Schubert et al., 2002). In other words, the classic pathophysiological model of the BG does not explain the origin of akinesia (see Rodriguez-Oroz et al., 2009 for review).

In an attempt to understand these contradictions, some authors have suggested that akinesia might also have non motor or non DA origins (Ballanger et al., 2007; Criaud et al., 2016b; Favre et al., 2013; Rodriguez-Oroz et al., 2009). In particular, it was suggested, mainly from behavioral laboratory studies, that executive dysfunction could play a role in akinesia (Albares et al., 2015b; Favre et al., 2013; Jahanshahi and Rothwell, 2017; Michely et al., 2012, 2015; Obeso et al., 2011). Executive processes refer to mechanisms dedicated to the higher-order control of behavior. This includes the ability to initiate, execute, monitor, and inhibit actions. However, the mechanisms underlying executive dysfunction are difficult to understand in PD because they are often masked by, or confounded with, motor features (Rodriguez-Oroz et al., 2009).

To sum up, the blurred borders of the clinical concept of akinesia and the difficulty to disentangle motor and executive processes make it particularly difficult to determine the neural bases of movement initiation disorders on the sole basis of clinical, neuropsychological and behavioral evaluations. By giving access to finer-grained mechanisms, functional imaging studies have the potential to reveal the dysfunctional brain processes that account for akinesia, within and beyond the motor circuitry. Here, we propose a critical review of the topic based on a systematic analysis of the available neuroimaging studies. Our hope is to identify common neural denominators across studies, despite the heterogeneous functions, definitions and methods used. No such review is currently available. It is intended to complement other recent reviews of the pathophysiology of akinesia focusing on DA denervation (Antonelli and Strafella, 2014; Jellinger, 2014) and subthalamic beta oscillations (Weinberger et al., 2009).

2. Methods

2.1. Literature selection

An electronic search was performed using the Web of Science and PubMed databases to collect studies on the neurofunctional bases of akinesia in PD until November 2018. The following search terms were used: ((Akin*) AND (Parkinson) AND (Imaging OR fMRI OR PET OR Activation OR Blood flow)) and all variants of these terminologies.

The inclusion criteria for this review were:

1) Brain activation abnormalities using PET rCBF or fMRI studies,
2) Including PD patients with akinetic-rigid subtypes (AR) or assessing akinetic symptoms,
3) Including a control group with healthy subjects (HC) and/or tremor-dominant PD patients (TD).
4) Performing at least one of the four contrasts AR > HC, HC > AR, AR > TD or TD > AR.

The exclusion criteria were:

1) Review articles,
2) Behavioral studies,
3) Conference abstracts,
4) Animal studies,
5) Case reports,
6) Metabolism or neurotransmission PET studies,
7) Studies focusing only on treatment x group interactions.

2.2. Data extraction and criterion-referenced assessment

Papers were analyzed according to four sets of criteria:

1) Characteristics of the Clinical groups

This includes the number of subjects, the clinical subtypes of PD patients (AR, TD), and the treatment status (ON/OFF Levodopa or Drug naïve).

2) Neuroimaging methods

The neuroimaging methods used to characterize dysfunctional neural activity were analyzed as a function of:

- The neuroimaging tool used (fMRI/SPECT/PET) and the nature of the signal captured (BOLD or rCBF);
- The control group used to infer the neural correlates of akinesia in AR patients (HC and/or TD)
- The data processing method used to infer neural activity (functional connectivity, task-related activation/block design, event-related activation);
- The strategy of analysis of the neural correlates (whole brain or regions of interest).

3) Characteristics of the behavioral task and rationale

Studies assessing the neural bases of akinesia associate clinical symptoms with discrete deficits in specific neural systems. This can rely on different strategies:

- Studies using no behavioral task: Resting state recordings allow linking clinical symptoms of akinesia to global and non-specific brain activity changes in defined neural systems, by assessing the intensity of spontaneous brain activity or resting state functional connectivity.
- Studies using a behavioral task: Task-based recordings allow

isolating the neural mechanisms of interest through specific behavioral designs, either by assessing specific event-related brain activity changes (event-related fMRI) or task-related motor activation (block designs) that differ between AR and HC.

We used several criteria informing about the strategy used by the authors: the author's explicit rationale and the behavioral task used to isolate the psychological mechanisms under scrutiny.

4) Neuroimaging results

For each study, the list of brain regions including the global maxima of the significant clusters was reported for the contrasts HC > AR and AR > HC. When available, results of the contrasts TD > AR and AR > TD were also reported. Resting state studies were analyzed apart from studies using behavioral tasks for task-related or event-related neuroimaging designs.

3. Results

3.1. Literature selection

1829 records were identified through database searching, including 1058 duplicates. 754 texts were excluded with respect to our criteria. Finally, only 17 full-texts (21 experiments) were included (Fig. 1).

3.2. Systematic analysis

Detailed results are presented in Table 1.

1) Characteristics of the Clinical groups

Most studies selected AR patients based on the mean AR score calculated with the corresponding items of the motor section of the Unified Parkinson's disease Rating Scale (UPDRS part III) ($N = 8$) (#1–3; #5–7; #12, #14). The other studies simply excluded PD patients with tremor ($N = 7$) (#9–11; #13; #15–17), considering akinesia as a major symptom of the disease. One study measured akinesia based on item #31 of the UPDRS-III (assessing global spontaneity of movements; #4). Only one study tested directly slowness in movement initiation in PD patients with a specific behavioral design (#8). Taken together, these studies comprised in average 19.1 ± 11.5 AR patients and 20.7 ± 16.9 HC. Detailed characteristics of the clinical groups are provided in Supplementary Table 1.

2) Neuroimaging methods

Fourteen studies used fMRI, two used SPECT and one used PET imaging. Seven studies performed resting state fMRI recordings (#1–7), while two recorded event-related activity (#8–9) and eight recorded task-related activity (block-design) (#10–17). Eight studies searched for the neural bases of akinesia with no a priori about brain regions (#1–2; #6; #10–13; #17); while nine studies searched for alterations in specific regions of interest (ROI) based on their rationale (#3–5; #7–9; #14–16).

3) Characteristics of the behavioral task and rationale

- Studies using no behavioral task:

Among the seven experiments collecting resting state data, three searched for alterations of intrinsic connectivity in akinetic PD patients with no a priori about specific psychological dysfunctions or brain regions (#1–2; #6), using Functional Connectivity Density (#1), Regional Homogeneity (ReHo) (#2) or Voxel-Mirrored Homotopic Connectivity (#6). One experiment searched for connectivity changes of regions involved in movement initiation (#4 – seed-based functional connectivity). One experiment focused on the functional connectivity of the BG network (#5). Two experiments probed the functional integrity of default mode network (DMN-), either by assessing the intensity of its spontaneous activity (#7) or by measuring its functional connectivity at rest (#3 – seed-based functional connectivity). These last two studies clearly assumed cognitive dysfunctions in akinetic PD patients (#3; #7).

- Studies using a behavioral task:

Most studies ($N = 10$) set-up behavioral experiments specifically designed to test the hypothesis that akinesia is a motor symptom. These studies used a motor task to reveal movement-related activations (joystick movements/sequential finger-to-thumb opposition movements/sequential finger tapping task/thumb pressing movements/timed movements), either by means of task-related (#10-17a) or event-related (#9) neuroimaging designs. Motor alterations associated with akinesia were evidenced using the HC > AR contrast in 8 experiments. Compensatory mechanisms of akinesia were revealed using the AR > HC contrast in 8 experiments.

Only two experiments tested the hypothesis that akinesia includes both motor and executive components (#8, #17b). Both studies focused on the pre-movement phase in order to capture the brain activity associated with motor preparation and executive control of movement initiation. One of the two experiments (whole brain PET) used a motor imagery task (#17b) while the other (ROI event-related fMRI) used a real, simple motor task (#8).

4) Neuroimaging results

Detailed clinical scores and neuroimaging data are displayed in Table 1.

- Studies using no behavioral task:

Resting state alterations in AR with respect to HC are found in a widely distributed, poorly reproducible network including the cerebellum, various frontal areas (primary motor cortex -M1-, medial prefrontal cortex -mPFC-, middle frontal gyrus -midFG-, inferior frontal gyrus -iFG-), parietal areas (inferior parietal cortex -IPC-, angular gyrus, cuneus), and different subcortical regions (putamen, caudate nucleus, thalamus, amygdala) (Fig. 2). The precuneus (#2–3, #5a), the posterior cingulate gyrus –PCC- (#2–3; #7), the occipital lobe (#3-5a), the thalamus (#2, #4-5a) and the insula (#2–4) were detected more consistently. Whole brain studies (#1–2, #6) with no a priori on the brain regions failed to find reproducible areas accounting for akinesia, with the exception of the midFG evidenced in two studies (#1–2). The two studies focusing on the DMN to test cognitive integrity in AR patients also failed to reveal reproducible dysfunctional brain regions, with the exception of the PCC (#3–7).

The direction of the effect in AR with respect to HC is also variable. Among the brain regions found in at least two different studies, contradictory results are reported in nine out of 15 cases. For instance, among the studies showing brain activity differences in the IPC, one reports increased activity in AR with respect to HC while two others report increased activity in HC with respect to AR.

An overlapping network is observed when considering TD patients rather than HC as a control population. Differences are found in the cerebellum, the PCC, the IPC, the primary somatosensory cortex, the superior and the inferior frontal gyri (only brain regions observed at least in two different studies are listed. For complete results, see Fig. 3). The direction of the effect is, however, as variable as in the AR vs. HC comparisons. There are two notable exceptions: The hypoactivity or hypoconnectivity of the cerebellum in AR found in four different studies (while the opposite pattern was found only once), and the hypoactivity

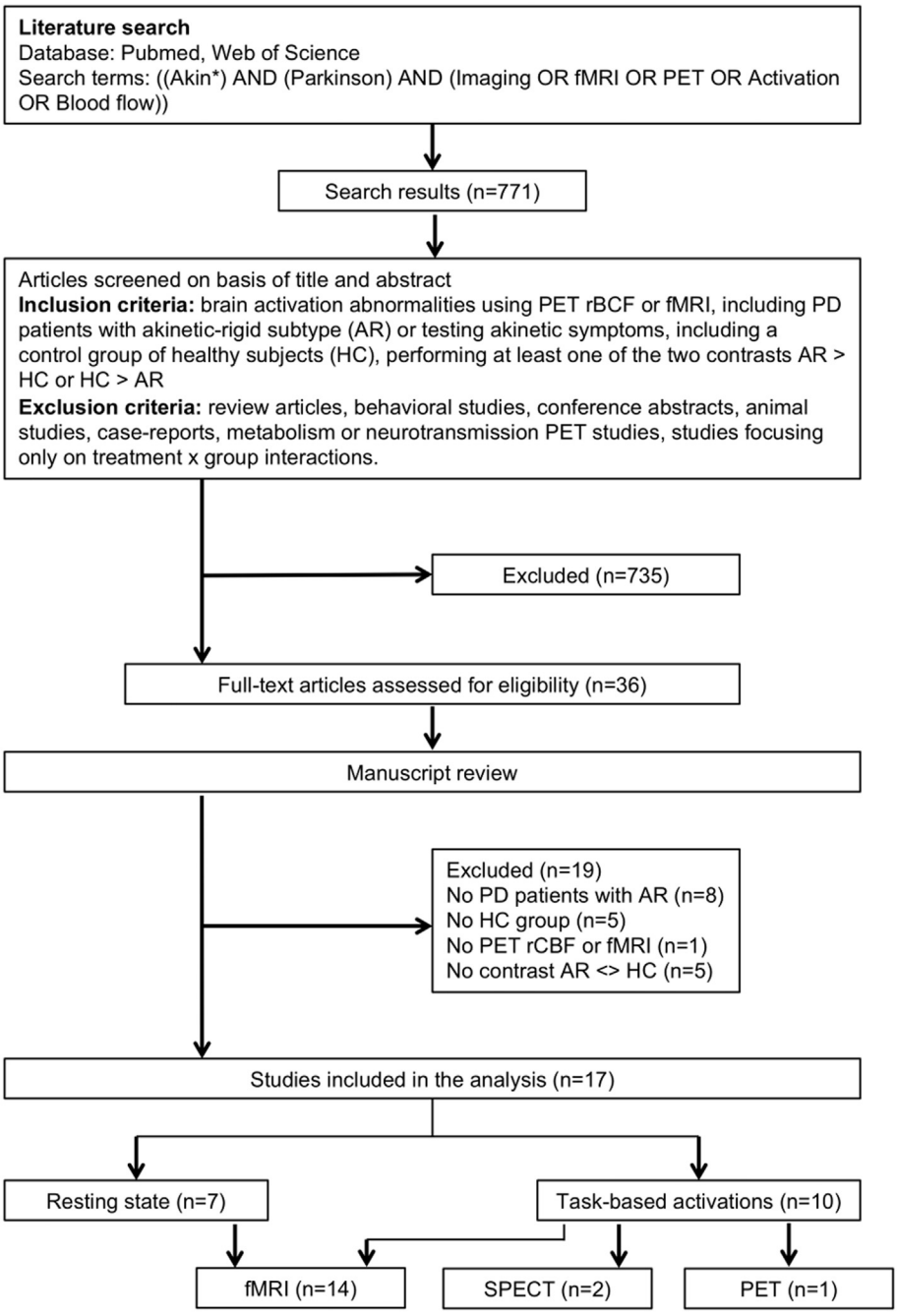

Fig. 1. Flow chart of publication selection for review, following PRISMA guidelines (Liberati et al., 2009).

of the PCC (reported in two different studies).

- Studies using a behavioral task:

Movement-related brain activity changes were found in a large network including the motor and supplementary motor cortices, the medial cortex (ACC, precuneus), the prefrontal cortex (dlPFC, iFG, frontal operculum), the visual cortex (lingual gyrus), the insula, the cerebellum, and subcortical regions (thalamus, insula, BG). Yet, these observations are poorly reproducible (Fig. 4). Consistent results were reported only for the cerebellum and the dlPFC, respectively found more activated in AR than HC (in four experiments; #12a-13; #16) and more activated in HC than AR (in four experiments; #11; #13; #17a-b). While changes in SMA activity were frequently reported (nine times; #8–13; #15–16), results are not fully consistent regarding the direction of the effect.

Only one study using a behavioral task has considered TD patients rather than HC as a control population (#14). No significant result was reported.

4. Discussion

The present systematic review pinpoints incompleteness and confounds that impede the identification of the neurofunctional bases of akinesia.

4.1. The terminology of akinesia

The first thing to come out from the present systematic analysis is that most papers (15 out of 17) are not backed up by a clear definition

Table 1
Systematic analysis of the functional neuroimaging studies included in the review.

Study		Population		Neuroimaging			Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
#1	Hu 2017	(−) AR dominant 25/26/25	OFF	fMRI BOLD	Intrinsic activity Functional connectivity density (FCD)	"to investigate the altered functional connectivity patterns of TD and AR subtypes"	(−)	*Whole brain*	AR > HC . HC > AR	(a) Increased global FCD in the frontal lobe (right inferior frontal gyrus/bilateral middle frontal gyrus); temporal cortex (right middle temporal gyrus) and left posterior lobe of the cerebellum in AR compared to HC. Ø
									AR > TD TD > AR	(a) Higher global FCD in AR in the left inferior frontal gyrus, right middle frontal gyrus, right superior frontal gyrus. (a) Lower global FCD in AR in the left cerebellum anterior lobule.
					Functional connectivity (FC) – Seed-based		(−)	*Seeds: regions showing differences in FCD between AR and TD*	AR > TD TD > AR	Ø (b) Lower FC in AR between the left cerebellum anterior lobule and the left primary somatosensory cortex, left superior frontal gyrus, right insula, right orbital inferior frontal gyrus.
#2	Zhang 2015	(−) AR dominant 27/26/20	OFF	fMRI rCBF	Intrinsic activity Functional connectivity, Regional Homogeneity (ReHo)	"to explore regional brain activity in TD and AR types during resting state to reveal distinct neural network in PD"	(−)	*Whole brain*	AR > HC	Increased ReHo in AR in the right amygdala, left putamen, bilateral angular gyrus, bilateral medial prefrontal cortex, bilateral middle frontal gyrus, right middle cingulate cortex and right supramarginal gyrus.
									HC > AR	Decreased ReHo in the left middle and posterior cingulate gyrus/precuneus, right insula, left fusiform gyrus, vermis 4/5 and bilateral thalamus.
									AR > TD TD > AR	Higher ReHo in AR in the left putamen, left primary somatosensory cortex, right superior temporal gyrus, right inferior frontal gyrus, left inferior parietal lobule. Lower ReHo in AR in the left posterior cingulate, left thalamus, left superior frontal gyrus, left primary motor cortex, bilateral cerebellum.

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Table 1 (*continued*)

Study		Population		Neuroimaging			Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
#3	Hou 2017	(−) AR dominant . 21/21	Drug naïve	fMRI .BOLD	Intrinsic activity Functional connectivity (FC) – Seed-based	"to test the functional connectivity of the DMN in cognitively unimpaired akinetic PD patients"	(−)	*Seeds and ROI: DMN*	. AR > HC HC > AR	Increased FC between the left medial prefrontal cortex, left posterior inferior parietal lobule and the cerebellum. Decreased FC between the posterior DMN and the cuneus, lingual gyrus and fusiform gyrus. Decreased FC between the anterior DMN and the middle and inferior frontal gyri, inferior parietal lobule and insula.
#4	Hensel 2018	Impairment to initiate spontaneous movements . PD patients . 60/72	ON	fMRI BOLD	Intrinsic activity Functional connectivity (FC) – Seed-based	"we hypothesized that akinesia was particularly related to connectivity changes with regions involved in movement initiation"	. (−)	*Seeds: Bilateral putamen, bilateral primary motor cortex, posterior medial frontal cortex – ROIs: seed-specific networks*	. AR > HC HC > AR	Ø [Within the putamen-specific network] Decreased FC between the putamen and the thalamus, putamen, pallidum. [Within the posterior medial frontal cortex-specific network] Decreased FC between the putamen and the bilateral intraparietal sulcus, posterior medial frontal cortex, dorsolateral prefrontal cortex, left inferior parietal lobule – Decreased FC between the posterior medial frontal cortex and the bilateral anterior insula, left dorsolateral prefrontal cortex – Decreased FC between the primary motor cortex and the pre-supplementary motor area. [Within the primary motor cortex-specific network] Decreased FC between the putamen, the primary motor cortex; and the bilateral supplementary motor area, primary motor and somatosensory cortex, superior parietal lobule, intraparietal sulcus, extrastriate visual cortex -Decreased FC between the putamen and the right dorsal premotor cortex – Decreased FC between the posterior

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Table 1 (*continued*)

Study		Population		Neuroimaging			Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/ HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
										medial frontal cortex and the bilateral primary somatosensory cortex, right superior parietal lobule. Negative correlation between akinesia scores and FC between the posterior medial frontal cortex and the right inferior parietal lobule within the posterior medial frontal AR dominant.
#5	Guan 2017	(−) AR dominant 49/52/57	Drug naïve or OFF	fMRI BOLD	Intrinsic activity Functional connectivity (FC) -Network-based	"differences of functional connectivity connecting with BG would be observed between the PD-AR and PD-TD"	(−)	*Basal Ganglia Network identified by ICA*	. AR > HC	Ø
									. HC > AR	(a) [Voxel-wised analysis] Reduced network-based FC in the bilateral thalamus, occipital lobule, precuneus [ROI-based analysis] Reduced network-based FC in the bilateral thalamus.
									AR > TD	Ø
									TD > AR	(a) [Voxel-wised analysis] Lower network-based FC in AR in the bilateral occipital lobule and right cerebellum posterior lobule [ROI-based analysis] Ø
					Intrinsic activity Eigenvector Centrality Mapping		(−)	*ROI: Bilateral caudate nucleus, putamen, pallidum, thalamus*	. AR > HC	(b) Enhanced eigenvector centrality in the right caudate nucleus and right thalamus.
									HC > AR	Ø
									AR > TD	Ø
									TD > AR	Ø
#6	Hu 2015	(−) AR dominant . 29/26/21	OFF	fMRI BOLD	Intrinsic activity Voxel-Mirrored Homotopic Connectivity (VMHC)	"we hypothesized that the VMHC alterations in motor-related cortical areas can be found in AR-PD group"	(−)	*Whole brain*	. AR > HC	Ø
									. HC > AR	Decreased VMHC values in the primary motor cortex.
									AR > TD	Higher VMHC in AR in the cerebellum posterior lobule.
									TD > AR	Ø
#7	Karunana- yaka 2016	(−) AR dominant . 17/24/15	ON	fMRI BOLD	Intrinsic activity	"to test the hypothesis that DMN integrity is different between TD and AR subtypes in PD"	(−)	*ROI: DMN*	. HC > AR	Decreased spontaneous brain activity in the left and right inferior parietal cortex and in the left posterior cingulate cortex within the DMN in AR compared to HC.
									. AR > HC	Ø
									AR > TD	Ø
									TD > AR	Lower spontaneous brain activity in AR in the left and

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Table 1 (*continued*)

Study		Population		Neuroimaging			Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/ HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
										right inferior parietal cortex, left posterior cingulate cortex within the DMN.
#8	Criaud 2016	Slowness in movement initiation PD patients without tremor . 12/15	ON	fMRI BOLD	Task-based activations Event-related	"to test the hypothesis that akinesia in PD is related to executive dysfunction (abnormal proactive inhibitory control)"	Motor Task Ext. *Simple reaction time task*	*ROI: Proactive Inhibitory Network*	. AR > HC	Increased pre-stimulus BOLD within several nodes of the proactive inhibitory network (caudate nucleus, precuneus, thalamus). Correlation between SMA activation and movement initiation latency. Increased movement initiation latency (akinesia) in AR compared to HC.
#9	Haslinger 2001	(−) AR without tremor 8/8	Drug naïve or OFF .ON	fMRI BOLD	Task-based activations Event- related	"to study BOLD cortical signal changes in M1/premotor areas associated with volitional limb movements in akinetic PD patients"	Motor Task Ext. . *Paced single joystick movements in a freely chosen direction*	*ROI: M1, Parietal and Frontal Motor Association Cortex*	. AR > HC HC > AR	Increased activation in bilateral M1 and SMA in AR-ON compared to HC. Increased activation in bilateral S1 M1 in AR-OFF compared to HC. Decreased activation in preSMA/SMA in AR-OFF and AR-ON compared to HC.
#10	Buhmann 2003	(−) AR without tremor 8/10	Drug naïve. ON	fMRI BOLD	Task-based activations Block design *(Modelling finger movements > delta functions convolved with HRF)*	"to explore movements' activations in akinetic PD patients"	Motor Task Ext. . *Simple paced random finger opposition task*	*Whole brain*	. HC > AR . UAH > AH* . ON > OFF	Hypoactivation of the M1 and SMA in AR compared to HC (drug-naïve). Hypoactivation of the contralateral M1 in AH compared to UAH (drug-naïve). Hyperactivation of the M1 contralateral to the affected hand and bilateral SMA after L-dopa (ON) compared to drug-naïve.
#11	Sabatini . 2000	(−) AR without tremor . 6/6	OFF	fMRI BOLD	Task-based activations . Block design	"to study differences in activation between akinetic PD patients and HC"	Motor Task Ext. *Complex sequential motor task*	*Whole brain*	. AR > HC HC > AR	Increased fMRI signal in the bilateral primary sensorimotor cortex, bilateral premotor cortex, inferior parietal cortex, caudal part of the SMA and ACC in AR compared to HC. Decreased fMRI signal in the rostral part of the SMA, in the right dorsolateral prefrontal cortex, in the left lateral premotor cortex and left inferior parietal cortex.
#12	Cerasa . 2006		OFF	fMRI BOLD	Task-based activations Block design	"to explore motor entrainment ability of akinetic PD patients"	Motor Task Ext./Int.	*Whole brain*	. AR > HC . HC > AR	(a) During synchronization phase, increased activity in

(*continued on next page*)

Table 1 (*continued*)

Study		Population		Neuroimaging			Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
		(−) AR dominant . 10/11					*Externally and internally timed movements*			the cerebellum, frontostriatal circuit (putamen, SMA, thalamus) and specific areas (right inferior frontal gyrus, insula, left lingual gyrus) in AR compared to HC. (b) During the continuation phase, increased activity in the cerebellum and the thalamus in AR compared to HC. Ø
#13	Yu . 2007	(−) PD patients without tremor . 8/8	OFF	fMRI BOLD	Task-based activations Block design	"to examine whether cerebellar and motor cortex hyperactivation is a compensatory mechanism for hypoactivation in the basal ganglia or is a pathophysiological response that is related to the sign of the disease"	Motor Task Ext. . *Automatic* vs. *cognitively controlled thumb pressing movements*	*Whole brain (ROI mask based on group comparison)*	. AR > HC . HC > AR	Hyperactivation of the cerebellum and the left primary motor cortex in AR compared to HC. Hypoactivation of the left putamen/right caudate, SMA and pre-SMA, right dlPFC in AR compared to HC.
#14	Lewis . 2011	(−) AR dominant . 8/14/9	OFF	.fMRI BOLD	Task-based activations . Block design	"to understand the clinical heterogeneity between TD and AR subtypes"	Motor Task Int. . *Internally-guided sequential finger tapping task*	*ROI: CTC/STC circuits*	. AR > HC . AR > TD	After adjusting for age, significant increase of the % of voxels activated in controlateral CTC circuits in AR compared to HC. Post-hoc t-tests within the CTC revealed no significance for any of the ROIs. After adjusting for age and side of symptom onset, significant increase of the % of voxels activated in ipsilateral STC and CTC circuits in AR compared to TD. Post-hoc *t*-tests revealed no significance for any of the ROIs.
#15	Rascol . 1994	(−) AR without tremor . 15;11/15	ON .OFF (between groups)	SPECT . rCBF	Task-based activations . Block design	"to assess whether the motor activation in the SMA is impaired or not when akinetic PD patients are treated with levodopa"	Motor Task Int. . *Sequential finger-to-thumb opposition movements*	*ROI: SMA. S1 M1*	. AR > HC . HC > AR	Hyperactivation of the ipsilateral S1 M1 in AR-ON compared to AR-OFF and HC. Hypoactivation of the SMA in AR-OFF compared to HC and AR-ON dopa. No changes on contralateral S1 M1 between AR and HC.
#16	. Rascol . 1997	(−) AR without tremor . 12;16/12	ON . OFF (between groups)	SPECT . rCBF	Task-based activations . Block design	"to compare rCBF changes induced by a motor task in the cerebellar hemisphere of	Motor Task Int. . *Sequential finger-to-thumb*	*ROI: CerebellumS1 M1, SMA*	. AR > HC	Overactivation in the ipsilateral cerebellum in AR-OFF compared to HC and AR-ON.

(*continued on next page*)

Table 1 (*continued*)

Study		Population		Neuroimaging			Methods		Results	
#	1st Author Year	Definition of akinesia. Symptoms. Subjects (AR/ HC/TD)	Treatment status	Tool. Signal	Type of activity. Data processing	Authors' rationale	Behavioral task	Regions of interest	Contrast	Brain regions showing significant differences
						akinetic PD or HC receiving or not levodopa"	*opposition movements*		. HC > AR	Hypoactivation in the SMA in AR-OFF compared to HC and AR-ON.
#17	Samuel . 2001	(−) PD patients without tremor . 6/6	OFF	PET . rCBF	Task-based activations . Block design	"to explore what is less activated in PD than in HC when executing or imaging movements"	Motor Task Ext. . *Paced single joystick movements in a freely chosen direction.* . Motor Imagery Task	*Whole brain*	. HC > AR	(a) For execution, reduced activation of the right dorsolateral prefrontal cortex and lateral premotor cortex, and bilateral thalamus and basal ganglia in AR compared to HC. (b) For imagery, reduction in dorsolateral and mesial frontal activation in the AR group compared to HC.

AR: Akinetic-Rigid dominant. HC: Healthy Controls. PD: Parkinson Disease. TD: Tremor Dominant. (−): no explicit definition of akinesia is provided. ON:ON levodopa – hyperdopaminergic state. OFF: from 6 to 24 h withdrawal of dopaminergic medication –hypodopaminergic state. Drug naïve: Patients who never experienced dopaminergic medication. Ext.: Externally driven. Int.: Internally driven -self-initiated-. AH: Affected –Akinetic- Hand. UAH: Unaffected -non-akinetic- Hand. CTC: Cerebello-Thalamo-Cortical Circuits. DMN: Default Mode Network. S1 M1: Primary Sensorimotor Cortex. SMA: Supplementary Motor Area. STC: Striato-Thalamo-Cortical Circuits. ACC: anterior cingulate cortex. Ø: No significant modification of activity/connectivity.

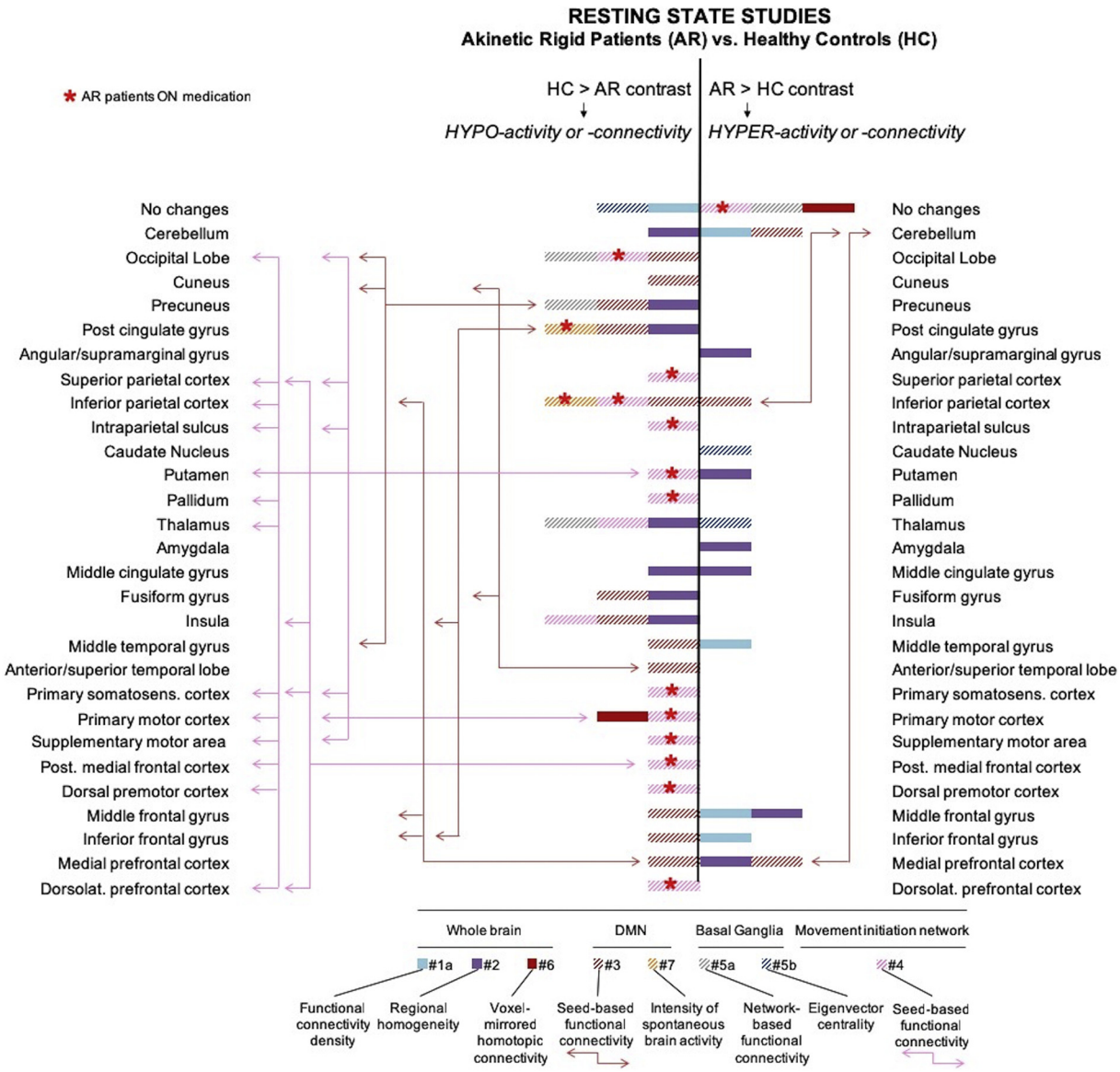

Fig. 2. Results of the neuroimaging studies using resting state approaches and comparing AR to HS subjects to assess the neural bases of akinesia. Arrows between two distinct brain regions indicate abnormal connectivity in seed-based functional connectivity studies. Studies assessing AR patients ON medication are indicated by red stars.

of akinesia (Table 1, supplementary Table 2). Rather, akinetic symptoms are just considered along with other predominant motor signs (Zaidel et al., 2009) to roughly distinguish AR from HC or AR from TD subtype of patients with PD (Buhmann et al., 2003; Cerasa et al., 2006; Guan et al., 2017; Haslinger et al., 2001; Hou et al., 2017; Hu et al., 2015, 2017; Karunanayaka et al., 2016; Lewis et al., 2011; Rascol et al., 1994, 1997; Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007; Zhang et al., 2015). Most of the studies reviewed here were intended to assess the neural correlates of these two disparate clinical subtypes of PD. In that respect, the use of derivatives of the term akinesia in these papers does not require, indeed, more detailed description. It is, however, still a problem for our purpose that the mean AR score confounds bradykinesia, hypokinesia and akinesia, and that it is not always computed from the same items across studies. A considerably more circumscribed definition is mandatory when it comes to relate specific akinetic clinical symptoms to behavioral markers and to neural and psychological mechanisms. On the one hand, studies comparing AR to TD and even more AR to HC highlight brain functional differences that cover a wide range of dysfunctions, beyond akinesia. That certainly explains part of the variability and contradictions regarding the dysfunctional neural networks associated with akinesia identified in the present review (Figs. 2–4). On the other hand, only one study has used a clear terminology based on Hallett's definition (Hallett, 1990) in combination with a behavioral design intended to capture specific markers of movement initiation disorders (Criaud et al., 2016b). Obviously, the results issued from this single study need to be reproduced to reach stronger scientific evidence (see limitations in supplementary Table 2). To summarize, although akinesia is considered a major feature of one of the most common and well documented neurodegenerative diseases, a definitive and unambiguous picture of its neural bases cannot emerge so far from the current literature. But there are both common denominators and interpretable differences between studies that raise important issues for future investigations.

4.2. Resting state modulations

The way networks are active or functionally connected during rest has the potential to inform about the functional integrity of human

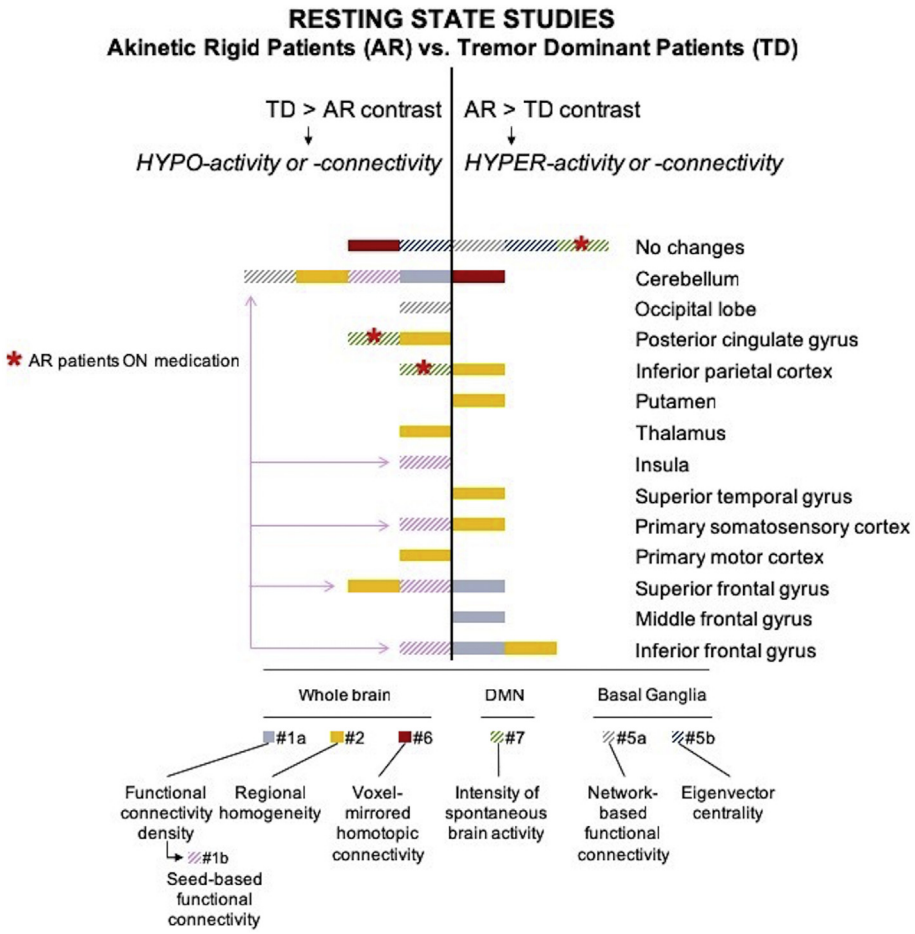

Fig. 3. Results of the neuroimaging studies using resting state approaches and comparing AR to TD subjects to assess the neural bases of akinesia. Arrows between two distinct brain regions indicate abnormal connectivity in seed-based functional connectivity studies. Studies assessing AR patients ON medication are indicated by red stars.

brain architecture in general, and about akinesia-related dysfunctional networks in PD in particular. We have identified only one study investigating spontaneous brain activity and six studies investigating different forms of functional connectivity at rest in AR patients.

Differences in the intensity of spontaneous brain activity between AR and HC but also AR and TD (Karunanayaka et al., 2016) can be observed in the left IPC and PCC (less intensity in AR). This represents an important advance with regard to former variable results about DMN functional integrity in PD (Delaveau et al., 2010; Ibarretxe-Bilbao et al., 2011; Krajcovicova et al., 2012; van Eimeren et al., 2009). Unfortunately, whole brain analyses have not been performed and differences have only been tested within the DMN. In other words, Karunanayaka's study (2016) has been very useful in identifying non-motor components of akinesia-related brain dysfunctions, but provided no clue about changes in the motor circuitry of AR patients with respect to other PD patients, which is not a closed issue.

Differences between AR and HC (or TD) in functional connectivity are observed in distributed but poorly reproducible brain areas, with the notable exception of the precuneus/PCC node, the insula, the thalamus and the occipital lobe. Besides common problems of imaging (heterogeneous data processing and paradigms, sample size, etc. See supplementary Table 2), the variability in the goals and methods used to probe altered intrinsic connectivity in AR patients (Table 1) is likely to explain part of the variability observed in the list of dysfunctional brain regions supporting differences between PD subtypes or between akinetic PD patients and matched controls. Abnormal local synchronization of spontaneous fMRI signals (ReHo) was found within various clusters in the medial cortical wall (mPFC, midFG, middle cingulate gyrus, supramarginal gyrus, PCC, precuneus, fusiform gyrus) and in subcortical regions (amygdala, putamen, thalamus) (Zhang et al., 2015). Alterations of large scale functional connectivity of the DMN (seed-based approach) were found between the mPFC and the IPC with the cerebellum, between the iFG and the mPFC, between the PCC with the insula and the iFG, between the precuneus and both the middle temporal gyrus and the lingual gyrus/cuneus (Hou et al., 2017). Quantitative aspects of synchronization as measured by means of functional connectivity density also highlight differences between AR and HC patients (Hu et al., 2017). Increased functional connectivity density in AR was found in the frontal lobe (midFG, iFG), in the temporal lobe (middle temporal gyrus), and in the cerebellum. Decreased connectivity between the hemispheres was found in AR at the level of the precentral gyrus (Hu et al., 2015). Reduced global connectivity -the correlation of each voxel time course with all other voxel time courses- was observed in the thalamus, the occipital lobule, and the precuneus within the BG network (Guan et al., 2017). Enhanced connectivity as indexed by eigenvector centrality values (i.e., the relative influence of a node in a network) was observed in the right caudate nucleus and the right thalamus (Guan et al., 2017). Although all these measures clearly represent different aspects of abnormal functional connectivity, one observation emerges from the global map provided these studies (Figs. 2, 3): it is likely that akinesia is not just a purely motor dysfunction, as all studies have identified AR-related dysfunctions that go way beyond the motor circuitry. The fact that the most reproducible results pinpoint dysfunctions of integrating hubs interacting with multiple brain networks involved in nonmotor aspects of behavioral control, like the precuneus/PCC node, the insula or the thalamus, is particularly supportive of this hypothesis. These key regions play a significant role in PD (e.g., Criaud et al., 2016a). Moreover, since an overlapping ensemble of brain regions has been identified in the studies which tested not only AR vs. HC contrasts but also AR vs. TD contrasts

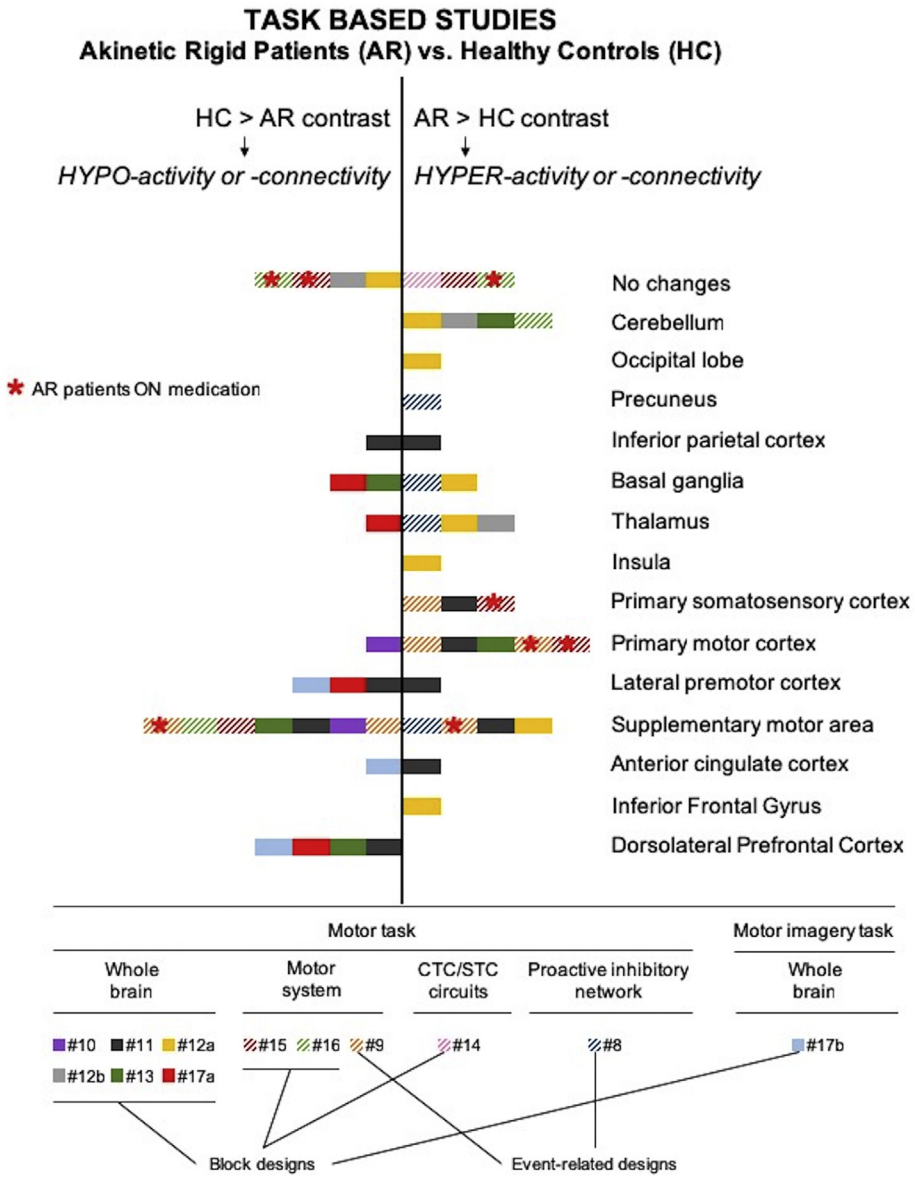

Fig. 4. Results of the neuroimaging studies using task-based approaches and comparing AR to HS subjects to assess the neural bases of akinesia. Studies assessing AR patients ON medication are indicated by red stars.

(Fig. 3), it is likely that the changes described above are not simply a broad effect of the disease, but actually an effect of PD subtype. Besides, studies performing whole-brain analyses (Hu et al., 2017; Hu et al., 2015; Zhang et al., 2015) did not even evidence consistent changes in the motor system.

4.2.1. *Dysfunctional vs compensatory mechanisms*

For a substantial part of the observations, resting activity and intrinsic functional connectivity results may appear contradictory between AR > HC and HC > AR contrasts (Fig. 2) or AR > TD and TD > AR contrasts (Fig. 3). However, these patterns are not necessarily in contradiction. Indeed, while decreased activity/functional connectivity is usually interpreted as a direct effect of the disease or condition, increased activity/functional connectivity is most often interpreted as the result of compensatory mechanisms by which BG-thalamo-cortical loop dysfunctions are overcome by the recruitment of other pathways (Hou et al., 2017). According to this debatable interpretation (Blesa et al., 2017), compensatory mechanisms would involve a widely distributed and poorly reproducible network (Fig. 2), including notably the cerebellum, the mPFC and the midFG (two occurrences each).

4.2.2. *Treatment status*

It is tempting to speculate that part of the inconsistencies mentioned above might be accounted for essentially by the treatment status: three studies tested patients OFF medication (Hu et al., 2015, 2017; Zhang et al., 2015), one study tested drug naïve de novo patients (Hou et al., 2017), one tested patients OFF medication or drug naïve (Guan et al., 2017), and two studies tested patients ON medication (Hensel et al., 2018; Karunanayaka et al., 2016). This is a substantial issue. Indeed, on the one hand DA medication is known to modulate the metabolism of the functional circuits subserving akinesia and rigidity (globus pallidus, thalamus, premotor cortex -PMC-, SMA and parietal association regions; Holtbernd and Eidelberg, 2012), and to improve the motor functions that partly contribute to reduce movement initiation latency (e.g., Favre et al., 2013). But on the other hand DA medication is also known for not reinstating a full normal pattern of movement initiation (Favre et al., 2013). The recent neuroimaging studies reviewed here testing AR patients ON medication (Hensel et al., 2018; Karunanayaka et al., 2016) report that DA medication does not reinstate a normal

pattern of brain activity and functional connectivity either (Figs. 2, 3). In other words, it is likely that there are other, non-DA dysfunctional neural mechanisms that contribute to akinesia (Albares et al., 2015b; Spay et al., 2018). Much more pharmacological neuroimaging investigations of resting states modulations building on the papers identified here are required to clarify this point, in particular studies testing directly the effect of DA medication.

4.2.3. Conclusion

The variability observed in the methods and in the results of resting state studies does not allow for any overall conclusions regarding the neural bases of akinesia. However, various clues are reported that raise the idea that abnormalities outside the motor network might be related to executive deficits in akinetic PD patients. Indeed, results pinpoint brain regions which are known to support executive control of movement initiation, including notably the PCC/Precuneus (Chikazoe et al., 2009; Criaud et al., 2017), the IPC (Criaud et al., 2017; Jaffard et al., 2008; Zandbelt et al., 2013), the insula (Chikazoe et al., 2009; Criaud et al., 2017), the mPFC (Jaffard et al., 2008) and the iFG (Aron, 2011; Aron et al., 2003; Jahfari et al., 2012; Zandbelt et al., 2013). Interestingly, most of these regions are also known to involve non-DA systems when engaged in these functions (Borchert et al., 2016; Buddhala et al., 2015; Chamberlain et al., 2009; Fox, 2013; Spay et al., 2018; Ye et al., 2015). This tentative explanation is consistent with previous studies on the neural bases of executive deficits in PD (Huang et al., 2007; Mattis et al., 2016; Pereira et al., 2014; van Eimeren et al., 2009).

4.3. Task-related and event-related brain activity changes

4.3.1. Dysfunctional mechanisms (akinesia-related hypoactivation)

Most experiments that recorded task-based modulations (eight out of twelve) searched for motor alterations, based on the common belief that akinesia is mainly a motor deficit (Buhmann et al., 2003; Cerasa et al., 2006; Haslinger et al., 2001; Rascol et al., 1994, 1997; Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007). According to the BG-thalamocortical circuit model, DA depletion in the nigrostriatal system induces hypoactivation in the motor and premotor circuits in akinetic PD patients compared to healthy controls, including the SMA, the lateral PMC and M1 (Alexander et al., 1990; Holtbernd and Eidelberg, 2012). This hypothesis has been tested in the eight experiments mentioned above by means of the HC > AR contrast, akinesia being simply associated with the absence of tremor. Results are quite inconsistent for most of the brain regions showing task-based and event-related brain activity changes (Fig. 4). Motor alterations are found in a widely distributed, poorly reproducible network including the motor/premotor cortices and associated subcortical areas (thalamus, BG), but also in the cerebellum, in different prefrontal areas (dlPFC, iFG) as well as in the ACC and in the insula. In these experiments, akinesia-related motor dysfunctions (hypoactivation in AR patients) are only consistent for the SMA across 6 experiments (Buhmann et al., 2003; Haslinger et al., 2001; Rascol et al., 1994, 1997; Sabatini et al., 2000), and for the dlPFC across half of the whole brain experiments (Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007). Again, despite inconsistencies about the extent of the observed modulations, studies using motor tasks to probe task-related and event-related brain activity changes in AR patients suggest that akinesia is not a purely motor dysfunction.

Only two experiments (out of twelve) considered the hypothesis that akinesia includes both motor and executive components. By focusing on the preparatory phase of movement (Criaud et al., 2016b; Samuel et al., 2001), they revealed akinesia-related alterations in the motor system (including the caudate nucleus and the lateral PMC), but also in other brain regions embracing the precuneus, the thalamus, the ACC and the dlPFC. Importantly, these regions are known to be part of an executive network involved in the inhibitory control of movement initiation (Blasi et al., 2006; Chikazoe et al., 2009; Jaffard et al., 2008; van Belle et al., 2014; Zandbelt et al., 2013). More precisely, Criaud and collaborators (2016b) proposed that akinesia in PD is associated with abnormal proactive inhibitory control, an executive function which supports the gating of movement triggering to avoid inappropriate or premature responses in uncertain contexts (Jahanshahi et al., 2015a; 2015b). According to this view, akinesia could be considered as a de-automation symptom resulting partly from an impairment of the ability to switch from controlled to automatic action (Albares et al., 2015b; Favre et al., 2013; Hikosaka and Isoda, 2010; Isoda and Hikosaka, 2007; Jahanshahi et al., 1995; Jahanshahi et al., 2015a; 2015b; Siegert et al., 2002). However, this hypothesis has been overlooked so far in neuroimaging studies of PD akinesia and requires further evidence.

An important part of the observed variability may be due to differences in the nature of the behavioral tasks used in the different studies. In particular, the differences observed between studies based on simple motor tasks (self-paced or internally triggered) and stimulus-response tasks (externally triggered) might be enlightening (Table 1). Simple motor tasks seem to induce effects confined to the SMA (hypoactivation in AR patients), the cerebellum and the primary sensorimotor cortex (hyperactivation in AR patients), or no changes at all (Cerasa et al., 2006; Lewis et al., 2011; Rascol et al., 1994, 1997). Conversely, stimulus-response tasks (externally triggered) involve a variety of brain regions outside the motor network (Cerasa et al., 2006; Criaud et al., 2016b; Samuel et al., 2001; Yu et al., 2007). Unfortunately, there is a strong bias, as identified in the quality check section (Supplementary Table 2). Studies using a simple motor task also applied ROI analyses centered on the motor system, making it impossible to conclude that only the more complex stimulus-response tasks involve dysfunctions outside the motor network.

It is noteworthy that most of the reviewed studies (Buhmann et al., 2003; Cerasa et al., 2006; Sabatini et al., 2000; Samuel et al., 2001; Yu et al., 2007) have been performed in the OFF-medication state. Only three studies have compared ON and OFF states but reported discordant results. Two of these studies (Rascol et al., 1994, 1997) suggest that DA restores normal SMA activity patterns in patients ON medication state with respect to OFF medication state and to healthy control subjects. The third one conversely suggests that residual deficits in M1 activity can be observed in the ON medication state (Haslinger et al., 2001). This, again, raises the issue of the purely motor and DA origins of akinesia. On the one hand, if one considers as Rascol et al. (1994, 1997) that DA restores normal activity in motor circuits, then the fact that akinesia is unsuccessfully alleviated by standard pharmacological treatments at a behavioral level (Favre et al., 2013; Fox, 2013; Jahanshahi et al., 1992; Schubert et al., 2002) strongly suggests a non-motor origin. On the other hand, if one considers as Haslinger et al. (2001) that the functional cortical deafferentation of motor regions associated with decreased input from the subcortical motor loop (see also Escola et al., 2003) is only partly reversible by levodopa treatment, then it is likely that non-DA dysfunctions are involved in akinesia. Unfortunately, all of these studies have used ROI approaches and focused on motor cortical dysfunctions. Future studies combining pharmacological approaches, whole brain analyses, and behavioral designs disentangling executive and motor functions might help addressing this open issue.

4.3.2. Compensatory mechanisms (akinesia-related hyperactivation)

Many studies which recorded task-based activations (eight out of twelve) also looked for hyperactivation of brain regions in akinetic PD patients compared to healthy subjects (contrast AR > HC), assuming that BG-thalamo-cortical loops dysfunctions are compensated for by the recruitment of parallel pathways (Sabatini et al., 2000). Again, some results are poorly reproducible (Fig. 4), like those pinpointing the motor cortex (M1, lateral PMC), the prefrontal cortex (iFC, dlPFC), the lateral and medial parietal cortex (iPC and precuneus), the visual cortex (lingual gyrus), the ACC and the insula. Yet, highest reproducibility is observed for the cerebellum (4 occurrences out of six studies performing cerebellar recordings: Cerasa et al., 2006; Lewis et al., 2011;

Rascol et al., 1997; Sabatini et al., 2000; Yu et al., 2007). These data are consistent with more general observations about compensatory mechanisms (Blesa et al., 2017). They are also consistent with the hyperconnectivity of the cerebellum observed at rest (Hou et al., 2017; Hu et al., 2017; Fig. 2). However, as highlighted in the recent review from Blesa et al. (2017), the substantiation of putative compensatory mechanisms remains weak. This might especially be the case for motor dysfunctions. For instance, Ballanger et al. (2009) observed that PD patients are able to improve dramatically motor performance, including movement initiation, by recruiting the contralateral cerebellum in externally driven urgent situations. However, by testing healthy controls, the authors also demonstrated that this form of compensatory mechanism, so-called paradoxical kineses, are not a hallmark of PD but a general property of the motor system (Ballanger et al., 2006). In other words, how specific to the disease and how specific to akinesia these mechanisms are is still highly disputable.

4.3.3. Conclusion

Although task-related and event-related brain activity changes are not highly reproducible across studies, results suggest that abnormalities within but also outside the motor pathways might induce motor and executive deficits that could contribute jointly to akinesia in PD patients.

5. Limitations

The reviewed studies represent a useful step towards refining the concepts and methods classically used to assess akinesia. However, the following limitations should be kept in mind as findings are interpreted.

Despite the scale of the problem and the total number of papers on the general topic of akinesia, few studies reached the criteria for being included (Fig. 1). This prevented us from performing any quantitative meta-analysis. The conclusions of this systematic analysis cannot rely on the use of statistical techniques for summarizing the results of all available studies into a single estimate. This weakens interpretation when common denominators are found between studies (i.e., movement-related hypoactivation in the motor cortex of AR patients). However, meta-analytical statistical methods would have ignored the brain activity which is poorly reproducible in terms of location, but which makes sense regarding the frequency of observation of the phenomenon (e.g., functional changes in different parts of the executive system). Often, variability in the exact location of brain functional differences is likely to be accounted for by the variability of the nature of the modulations that were assessed (e.g., intensity of intrinsic activity vs. functional connectivity density vs. ReHo vs. seed-based functional connectivity for resting state studies).

Due to the level of inaccuracy and confusion related to the terminology of akinesia, there are strong potential confounds in the imaging results. Most studies are referring to the AR subtype of PD, defined by paucity and slowness of movement accompanied by muscle stiffness. However, the set of dysfunctions which are specific of this subtype form a syndrome (Donaldson et al., 2012) that includes more disorders than the sole dysfunction of movement initiation mechanisms. Yet, there is no mean to disentangle these confounds in the reviewed studies. Accordingly, the results pinpoint neural correlates rather than comprehensive neural bases of akinesia, and the causal links between brain dysfunctions and clinical symptoms inferred from these studies remain speculative.

6. Open issues and future directions

Given the inconsistency of concepts and results, tentative conclusions on the neural bases of akinesia would be somewhat hazardous. However, the clues provided by the neural correlates analyzed in this review raise major issues for future studies.

6.1. Characteristics of the clinical group: how to define akinesia?

A consensus on the neurofunctional bases of akinesia requires a unified use of terminology for this specific disturbance of voluntary movement, but there are still obstacles to overcome. First, the term akinesia is used at different conceptual levels: as a classifying term to identify subtypes of movement disorder like most of the studies reviewed here, and as a descriptive term to depict particular symptoms. Second, from a clinical point of view there is a tendency to group clinical signs, and consequently to use unique terminology whereas these signs represent clusters of symptoms (Schilder et al., 2017; Pellegrino and Thomasma, 1981). From an epistemological point of view, this contributes to form a substantial obstacle (Smith, 2016) in clinical research. This is often the case, for instance, when direct links between DA depletion and movement disorders are assessed. A clear definition of akinesia would help targeting more precisely the multiple mechanisms that are potentially dysfunctional in this multifaceted disease. It would help developing more sophisticated models for assessing brain-behavior relationships in PD neuroimaging studies.

6.2. Neuroimaging methods: How to reveal akinesia?

Appropriate behavioral designs and markers are required to isolate the neural mechanisms that play a direct role in movement initiation, and to measure their efficiency. Using advanced psychological models -and associated designs- of movement preparation and executive control should help making predictions about the nature, the dynamics or the localization of the brain signals that are most likely to inform about the neural correlates of akinesia (e.g., Criaud et al., 2017). This is crucial for setting-up adapted event-related neuroimaging designs. In particular since the present review has pinpointed: (1) the underuse of this type of approach, and (2) the possibility that akinesia does not only rely on motor dysfunctions. For instance, assessing the executive mechanisms that gate movement initiation in uncertain contexts in order to avoid premature or erroneous responding – a function which might cause akinesia when disturbed (Jahanshahi et al., 2015a, 2015b)- requires: (1) the manipulation of the relative probability of the stimuli in the experimental design, and (2) the analysis of the brain activity occurring before a movement is initiated (e.g., Criaud et al., 2016b). Additionally, specific behavioral markers like reaction time or omission rate can be used as covariates in functional data processing in order to select the brain modulations that play a direct role in behavioral changes (e.g., Albares et al., 2015a; Albares et al., 2014). The same rationale applies to standard clinical scores, which must also be included in data processing models in order to relate the clinical severity of PD symptoms to behavioral manifestations and specific brain activity changes. Only then should the large and inconsistent inventory of neural correlates of akinesia be reduced to a shorter list of reliable candidates forming the neural bases of akinetic symptoms.

Finally, the hypothesis of an executive origin of akinesia raised in the present review calls for using complementary neuroimaging tools. Indeed, executive control strongly relies on inhibitory functions (Heyder et al., 2004; Hofmann et al., 2012; Miyake et al., 2000; Norman and Shallice, 1986). However, no single neuroimaging method based on blood flow measurements can disentangle the time-course of concurrent excitatory and inhibitory mechanisms (Logothetis, 2008). Disentangling the executive and motor dysfunctions of akinetic symptoms may require the use of other techniques such as MEG and EEG, which offer the possibility to identify inhibitory activity through spectral analyses (Albares et al., 2015a). Since recent developments now offer optimal solutions for separating and localizing the brain electrical sources of activity that are mixed on the scalp (e.g., Lio and Boulinguez, 2013, 2018), EEG might represent a promising alternative to the standard neuroimaging methods reviewed here, at least for identifying cortical dysfunctions.

6.3. Pharmacological neuroimaging: How to reveal the neurochemical bases of akinesia?

It is clear that other neurotransmitters than DA play a role in the pathophysiology of PD (Bohnen et al., 2018; Braak et al., 2004; Delaville et al., 2012; Faggiani and Benazzouz, 2017; Fornai et al., 2007; Pahapill and Lozano, 2000; Politis et al., 2014). Yet, non-DA therapeutic strategies are still difficult to develop (Fox, 2013; Freitas and Fox, 2016). It is likely that the lack of neurocognitive footing in clinical neuroimaging studies does not help for distinguishing the neural mechanisms that rely on DA neurotransmission from those that rely on other systems. We especially think about the noradrenergic system, which might be involved in the functioning of BG-thalamo-cortical loops and executive functions (Albares et al., 2015b; Chamberlain et al., 2009; Faggiani and Benazzouz, 2017; Spay et al., 2018), but also about the serotoninergic (Carli and Invernizzi, 2014; Miguelez et al., 2014) and the cholinergic (Bohnen and Albin, 2011) systems. Here, we suggest that future pharmacological neuroimaging designs, whatever goal they are intended for –e.g., testing dose-dependent effects in DA-medicated patients or non-DA pharmacological agents in healthy subjects-, should comply with the general recommendations described above to reveal the neurochemical bases of movement initiation and related disorders. Given the multidimensional complexity of movement disorders in general, and akinesia in particular, future neuroimaging studies should not settle on linking vague clinical subtypes and/or pharmacological challenges to broad and unspecific brain activity modulations. Rather, future studies should target specific neural mechanisms by means of adapted empirical designs and behavioral markers. More sophisticated behavioral tasks (e.g., Criaud et al., 2016b, Criaud et al., 2017) combined with the use of movement analysis technologies (e.g., Dai et al., 2015; Salimi-Badr et al., 2017; Varriale et al., 2018) to detect and quantitate akinesia might prove useful to better isolate, and then image, the processes that are directly linked to movement initiation disorders. With these conditions in place, future studies will get more chances to extricate the complex interactions that form the neural and neurochemical bases of akinesia.

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Supplementary data

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