Peer-reviewed version available at Nutrients 2018, 10, 708; doi:10.3390/nu10060708

Systematic Review

Changes of colonic bacterial composition in Parkinson's Disease and other neurodegenerative diseases

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Abstract: In the last years evidence has emerged that neurodegenerative diseases (NDs) are strongly associated with the microbiome composition in the gut. Parkinson's disease (PD) is the most intensively studied neurodegenerative disease in this context. In this review, we performed a systematic evaluation of published literature comparing changes in colonic microbiome in PD to the ones observed in other NDs including Alzheimer's Disease (AD), Multiple system atrophy (MSA), Multiple sclerosis (MS), Neuromyelitis optica (NMO) and Amyotrophic lateral sclerosis (ALS). To warrant comparability of different studies, only human case-control studies were included. Several studies showed an increase of *Lactobacillus*, *Bifidobacterium*, Verrucomicrobiaceae and *Akkermansia* in PD. A decrease in PD was observed of *Faecalibacterium spp.*, *Coprococcus spp.*, *Blautia spp.*, *Prevotella spp. and* Prevotellaceae. On low taxonomic resolution, like phylum level, the changes are not disease specific and inconsistent. However, on higher taxonomic resolution like genus or species level, a minor overlap was observed between PD and MSA, both alpha synucleinopathies. We show that a methodical standardization of sample collection and analysis is necessary for ensuring the reproducibility and comparability of data. We also provide the evidence, that assessing the microbiota composition at high taxonomic resolution, reveals changes in relative abundance, that may be specific or characteristic for one disease, or a disease-group and might evolve discriminative power. The interactions between bacterial species and strains and moreover the co-abundances must be more deeply investigated before assumptions of the effects of specific bacteria on the host can be made with certainty.

Keywords: Parkinson's disease; gut microbiome; neurodegenerative diseases; microbiota-gut-brain-axis

1. Introduction

The causes of the heterogenic group of neurodegenerative diseases (NDs) are still unknown but several contributing factors including genetic and lifestyle factors and age-related aberration of health are likely to play a role. The pathology in PD was found to start in more caudal parts of the central nervous system (CNS) or even in the enteric nervous system moving the gut and its interaction with CNS into a sudden spotlight [1-3]. While some researchers question whether PD begins in the gut, a potential role of gut microbiome in PD pathology is undisputed [4].

PD is a neurodegenerative disease with the hallmark of cardinal progressive motor symptoms such as tremor, muscular rigidity, postural instability and bradykinesia, mostly additionally accompanied by nonmotor symptoms. Characteristic are furthermore the alpha synuclein containing aggregations, named Lewy bodies, that can be found in the central, autonomous and enteric nervous system [5].

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Indeed, the microbiota greatly modulates the function and homeostasis of the gut and the human health beyond the gut. There are up to hundred times more microbial genes, named the microbiome, than human genes in one individual [6]. The largest part of humans' microbiota is gathered in the gut and the community compromises of more than 10 trillion cells and up to thousand different microbial species per individual [7]. This complex community is responsible of a myriad of different metabolic, immunologic and homeostatic functions [8]. The different taxa interact, rely on and out crowd each other, leading to distinct compositions in various stages of human health and disease [9,10] and age [11,12]. In animal studies different potential mechanisms of neurodegenerative disease were discovered, where the gut microbiome played a key role to affect brain physiology and function. The gut-brain-axis is a bidirectional communication pathway comprising direct neural, endocrine and immunological mechanisms [13]. The gut-brain-axis may be implicated in alpha synuclein mediated pathology, which is supposed to spread from the gut to the brain [14]. Also, in humans, there is some evidence supporting the role of the gut-brain-axis in PD pathophysiology, for example that truncal vagotomy reduces the risk for PD [15]. Moreover, also a healthy intestinal barrier function seems crucial for maintaining neurological health [16]. In animal models of NDs a distinct and discriminative microbial composition was found, e.g. for ALS [17,18] and AD [19]. Consequently, some attempts were made to assess the microbial composition in human patients suffering from neurodegenerative diseases. For this purpose, different methodical approaches were used such as 16S rRNA or 16S cDNA sequencing, metagenomic shotgun sequencing and different microarray assessments.

This review aims to summarize changes in the microbiota composition assessed by these genetical investigations in human patients with NDs. This is, to our knowledge unique, in the broad coverage of findings of microbiome in patients of different NDs. Since the largest part of gut microbiota is comprised of bacteria and because their role in NDs is supported by the highest scientific evidence, while the term also includes fungi and viruses, this review concentrates on the compositional changes of the bacterial taxa. We show that analysis of colonic bacterial composition at the highest possible resolution may be predictive for PD and discriminate PD from other neurodegenerative diseases [13,20-24]. Methodical standardization procedures ensure comparability of studies.

2. Materials and Methods

The key-question of this review was whether PD patients present specific taxonomic changes in gut microbiota discriminating them from other NDs and from healthy controls? This is a systematic review of human case-control-studies, summarizing the findings of original studies published in the last five years (01.01.2013-31.12.2017), during which the most research on this topic is performed.
PubMed databank and online books were searched due to combining the MESH-Terms of the following NDs (as focused by JPND, Eu Joint Programme – Neurodegenerative Disease Research: Parkinson's Disease, Alzheimer's Disease, Prion disease, Motoneuron diseases, Huntington disease, Spinocerebellar ataxia, Spinal muscular atrophy and additionally Multiple system atrophy, Multiple sclerosis, Neuromyelitis optica, Amyotrophic lateral sclerosis) combined with following terms:

"microbiome", "microbiota", "bacteria", "bacterial", "composition", intestine, "intestinal", "gut"

We concentrated on bacterial taxa and excluded results regarding fungi, archaea and viruses.
Articles which fulfilled the following criteria were included in the comparison:

- subjects in the case groups had a diagnosis for the disease given by an expert.
- human case-control-studies
- at least one part of the study analysed the gut microbiome in a cross-sectional manner compared to healthy controls
- faeces collection to generate a sample probe
- microbiota analysis by amplification sequencing methods or hybridisation on microarrays: Phylochip G3, YIFscan
- published in peer-reviewed journals

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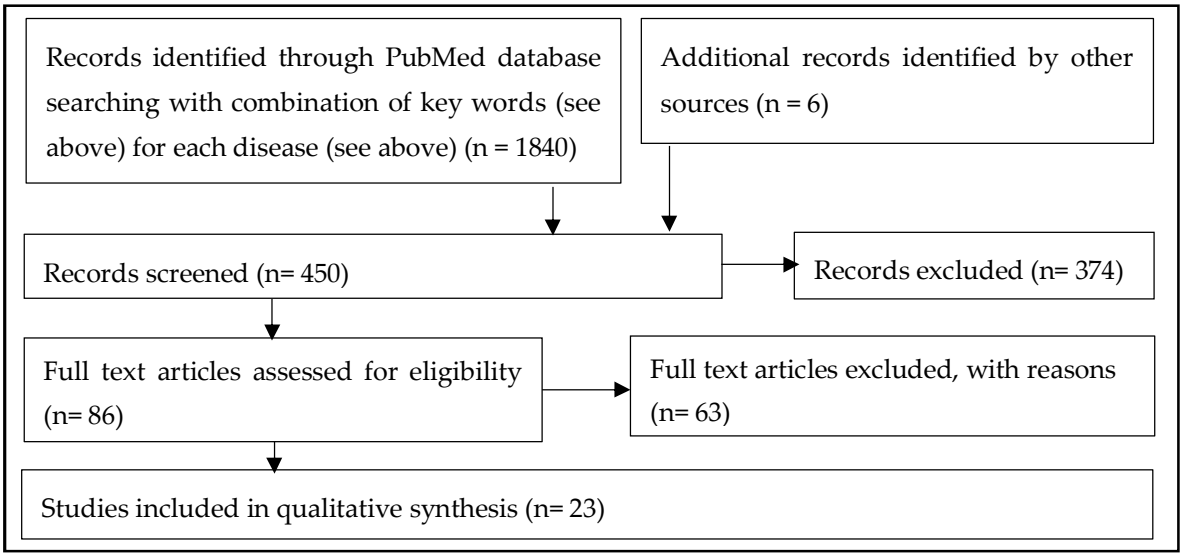
- paper available in English language

Animal studies were excluded, because our review did not aim at proving a possible mechanistic explanation of neurodegeneration. Our aim was rather identifying the exact taxa, that plays a role in NDs, because such information may be used as potential biomarkers and thus be clinically relevant for early disease diagnosis. Thus, potential confounding influences of different host species is ruled out by comparing only using human data. The focus of our review is PD, but the results of all mentioned NDs can be seen in the additional table A1 in the Appendix A. To our knowledge no other review to date provides such a comprehensive overview of the observed relative microbiome changes in abundance in PD as well as in other NTs such as Alzheimer's Disease (AD), Multiple system atrophy (NSA), Multiple sclerosis (MS), Neuromyelitis optica (NMO) and Amyotrophic lateral sclerosis (ALS).

Figure 1. Methodical approach of systematic review due to PRISMA criteria. (PRISMA criteria [25])



3. Results

Ten case-control-studies enrolling PD patients were included in the analysis. Five studies used the Illumina Miseq sequencing methods [26-30], while two studies used Illumina Hiseq sequencing method [31,32]. One study used the Roche 454 GS FLX Titanium sequencing method [33]. Two included studies used other taxonomic identification and quantification methods: Yakult Intestinal Flora-SCAN (YIF-Scan) [34] or 96-well block of the ABI PRISM 7900HT Sequence Detection System [35]. The last two methods only assess targeted microbial taxa and are used to reproduce previously reported findings, whereas the methods of the other eight studies assess the whole microbiome and may detect surprising unknown species.

In the majority of publications, where information on Alpha diversity/richness was given, no significant difference between healthy controls and PD cases were found. Whereas in all reports, where information on overall beta-diversity was presented, it differed significantly between healthy controls and PD.

Table 1 Richness, alpha-diversity, beta-diversity

Reference	[34]	[35]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Indexes/ Method	YF	PR	Ill Miseq					Ill Hiseq		Ro
Faecal bacterial counts	>	n	n	n	n	n	n	n	n	n

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Alpha diversity/Richness on at least one taxonomic level (chao 1 index, *other indexes)	n	n	>	n	-	-	<*	-*	n	-
Overall Beta diversity (weighted Unifrac, *other indexes)	n	n	sd	sd	sd*	sd*	n	sd*		sd

Table 1. This table shows the significant differences in faecal bacterial counts, alpha diversity/richness and beta diversity between healthy controls (HC) and Parkinson cases (PD).
> symbolizes a higher abundance in HC when compared to PD
< symbolizes a lower abundance in HC when compared to PD
- symbolizes, that no statistical significant difference was found between HC and PD
sd indicates a statistically significantly difference
n symbolizes, that no information was given. The methods used by the studies are Yakult Intestinal Flora-SCAN (YF), 96-well block of the ABI PRISM 7900HT Sequence Detection System (PR), Illumina Miseq sequencing (Ill Miseq), Illumina Hiseq sequencing (Ill Hiseq), Roche 454 GS FLX Titanium sequencing (Ro).

3.1 Taxonomic changes

Taking the ten publications together, changed relative bacterial abundances between HC and PD were observed on all taxonomic levels. A table is provided for each phylum, which showed changes between HC and PD in at least one study. Only significant changes ($p<0.05$), which underwent a statistical analysis and correction by the authors of the original study, were included in the tables. The tables only show changes on phylum, family, genus, species or operational taxonomic unit (OTU) levels, always in the highest taxonomic resolution, that the authors of the study provided. The few additional changes on class or order level will be specifically described in the discussion. Significant changes in relative abundances were observed only within five phylae: namely Firmicutes, Actinobacteria, Bacteroides, Verrucomicrobia and Proteobacteria.

3.1.1 Firmicutes

The most changes in relative abundance of colonic microbial taxa were observed within the Firmicutes phylum. Single studies found changes in unclassified Firmicutes and in various families and genera (Table 2). Significant increase of genus *Lactobacillus* [26,27,34], decrease of genus *Faecalibacterium* or species *Faecalibacterium prausnitzi* or OTU's that belong in this category [26,27,29,35], the decrease of genus *Coprococcus* [30] or species *Coprococcus eutactus* [26] or OTU [27] belonging in this category and decrease of genus *Blautia* [29,30] or species *Blautia glucerasea* [26] or OTU belonging in this category [27] were reported and confirmed in PD.

Table 2 Firmicutes

Reference	[34]	[35]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Taxa/ Method	YF	PR	Ill Miseq					Ill Hiseq		Ro
Unclassified Firmicutes (unclass.)								<		
Firmicutes unspecified (unspec.)							>			
Lactobacillaceae unspec.		>		<	<					<

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Lactobacillus, m=mucosae, g=gassero, c=caseo, f=fermentum, re=reuteri, ru=ruminis,	< (+g, c, f, re, ru)		< (+m)	<						
Enterococcaceae unspec		>			<	<				
Enterococcus						<				
Ruminococcaceae unclassified				<						
Ruminococcaceae OTU 4439469				< (1o)						<
Ruminococcus, b=bromii, c=callidus			< (b)	> (c)			>			
Papillibacter c=cinnamivorans			< (c)							
Faecalibacterium, p=prausnitzi		> (p)	>	> (o2)		>				
Lachnospiraceae unclassified				> (o3)						
Lachnospiraceae unspec				>						
Roseburia				>(+o2)			>			
Coprococcus, e=eutactus			> (e)	>(o1)			>			
Blautia, g=glucerasea			> (g)	> (+o1)		>	>			
Dorea, l=longicatea			> (+l)							
Catabacteriaceae Catabacter, h=honkongenesis			<(+h)							
Clostridiaceae Anaerotruncus									<	
Clostridium, c=coccoides, s=saccharolyticum	> (c)							> (s)		
Eubacteriaceae, [candidatus stoquefichus massiliensis]			>							
Erysipeltrichoceae unspec.						<				
Eubacterium, b=biforme								> (b)		
Christensenellaceae unclass.				<						
unspec				<						

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Christensenella, m=minuta			< (+m)							
Oscillospiraceae, oscillospira			<				<			
Streptococcaceae, unspec						<				
Streptococcus						<				
Acidaminococcaceae, Acidaminococcus						<				
Veillonellaceae unspec						<				
Veillonellaceae, Megamonas						<				
Veillonellaceae Megasphera						<				
[Tissierellaceae] unspec.				<						

Table 2. This table shows the significant relative changes in Firmicute phyla between PD patients (PD) and healthy controls (HC), that were assessed by the ten summarized Parkinson's disease studies.
> symbolizes a higher abundance in HC when compared to PD
< symbolizes a lower abundance in HC when compared to PD
- equals, that no significant change in PD compared to HC was found with the chosen methodological approach.
o1, 2, 3 symbolize, that one, two, three OTU's of the taxa were significantly changed in PD compared to HC
+ indicates that a change in PD compared to HC on the genus and on the species level was found.
The methods used by the studies are Yakult Intestinal Flora-SCAN (YF), 96-well block of the ABI PRISM 7900HT Sequence Detection System (PR), Illumina Miseq sequencing (Ill Miseq), Illumina Hiseq sequencing (Ill Hiseq), Roche 454 GS FLX Titanium sequencing (Ro).

3.3.2. Actinobacteria

In all studies in which changes in relative abundance of or within the phylum Actinobacteria were reported, PD patients reproducibly showed an increase of relative abundance compared to HC [26,27,29,35] (Table 3). The increase of genus *Bifidobacterium* was reproduced in three studies [26,27,35].

Table 3 Actinobacteria

Reference	[34]	[35]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Taxa/ Method	YF	PR	Ill Miseq					Ill Hiseq		Ro
Unspec						<				
Bifidobacteriaceae, Unspec.				<						
Bifidobacteriaceae, Bifidobacterium		<	<	<						
Coriobacteriaceae, Unspec						<				

Table 3. This table shows the significant relative changes in Actinobacteria between PD patients (PD) and healthy controls (HC), that were assessed by the ten summarized Parkinson's disease studies.

> symbolizes a higher abundance in HC when compared to PD
< symbolizes a lower abundance in HC when compared to PD
- equals, that no significant change in PD compared to HC was found with the chosen methodological approach.
o1, 2, 3 symbolize, that one, two, three OTU's of the taxa were significantly changed in PD compared to HC
+ indicates that a change in PD compared to HC on the genus and on the species level was found.
The methods used by the studies are Yakult Intestinal Flora-SCAN (YF), 96-well block of the ABI PRISM 7900HT Sequence Detection System (PR), Illumina Miseq sequencing (Ill Miseq), Illumina Hiseq sequencing (Ill Hiseq), Roche 454 GS FLX Titanium sequencing (Ro).

3.3.3. Bacteroidetes

The published data for the phylum Bacteroidetes was highly variable between the different reports. The potential trend of decreased Bacteroidetes on phylum level [29,35] and decreased genus *Bacteroides* [26] or species *Bacteroides fragilis* [34] was observed in the opposite direction by one publication [30]. Three studies found a significant reduction of Prevotellaceae family [24,35] or the genus *Prevotella* [26,31]. One study found a similar but not significant decrease of Prevotellaceae [35]. Hill-Burns et al, 2017, did not confirm these findings, but observed an increase in one OTU that belongs to the genus *Prevotella* [27].

Table 4 Bacteroidetes

Reference	[34]	[35]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Taxa/ Method	YF	PR	Ill Miseq					Ill Hiseq		Ro
Unspec		>				>	<			
Bacteroidaceae, Bacteroides c=coprocola, d=dorei, f=frgailis, p=phlebeus, m=massiliensis	> (f)		> (+m, c, d, p)				<			
Prevotellaceae, Unspec										>
Prevotellaceae, Prevotella, co=copri			> (+co)	< (o1)				> (+co)		
Porphyromonadaceae, Parabacteroides				<						
Porphyromonadaceae, Barnesiella (in the original article classified as Barnesiellaceae)					<					
Rickenellaceae, Alistipes, s=shahii								< (s)		

Table 4. This table shows the significant relative changes in Firmicute phyla between PD patients (PD) and healthy controls (HC), that were assessed by the ten summarized Parkinson's disease studies.
> symbolizes a higher abundance in HC when compared to PD
< symbolizes a lower abundance in HC when compared to PD
- equals, that no significant change in PD compared to HC was found with the chosen methodological approach.
o1, 2, 3 symbolize, that one, two, three OTU's of the taxa were significantly changed in PD compared to HC

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+ indicates that a change in PD compared to HC on the genus and on the species level was found.
The methods used by the studies are Yakult Intestinal Flora-SCAN (YF), 96-well block of the ABI PRISM 7900HT Sequence Detection System (PR), Illumina Miseq sequencing (Ill Miseq), Illumina Hiseq sequencing (Ill Hiseq), Roche 454 GS FLX Titanium sequencing (Ro).

3.3.4. Verrucomicrobia

Like as within the phylum of Actinobacteria, also in Verrucomicrobia all reported changes were increases of certain microbial taxa [27,30-33] (Table 5). Within the phylum Verrucomicrobia there was a high overlap of the results from the different PD studies. The relative abundance of Verrucomicrobiaceae family [27,30,32,33] and *Akkermansia* genus [27,30-32] were increased each in four studies.

Table 5 Verrucomicrobia

Reference	[34]	[35]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Taxa/ Method	YF	PR	Ill Miseq					Ill Hiseq		Ro
Unspec									<	
Verrucomicrobiaceae, Unspec				<			<		<	<
Akkermansiaceae, Akkermansia, m=muciphila				<			<	< (+m)	<	

Table 5. This table shows the significant relative changes in Firmicute phyla between PD patients (PD) and healthy controls (HC), that were assessed by the ten summarized Parkinson's disease studies.
> symbolizes a higher abundance in HC when compared to PD
< symbolizes a lower abundance in HC when compared to PD
- equals, that no significant change in PD compared to HC was found with the chosen methodological approach.
o1, 2, 3 symbolize, that one, two, three OTU's of the taxa were significantly changed in PD compared to HC
+ indicates that a change in PD compared to HC on the genus and on the species level was found.
The methods used by the studies are Yakult Intestinal Flora-SCAN (YF), 96-well block of the ABI PRISM 7900HT Sequence Detection System (PR), Illumina Miseq sequencing (Ill Miseq), Illumina Hiseq sequencing (Ill Hiseq), Roche 454 GS FLX Titanium sequencing (Ro).

3.3.5. Proteobacteria

Single studies found changes in relative abundance within the Proteobacteria, Alpha-proteobacteria- and Gammy-Proteobacteria-phylae. None of these findings were reproduced by other studies, apart from the increase in Enterobacteriaceae family in two studies [29,35].

Table 6 Proteobacteria

Reference	[34]	[35]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Taxa/ Method	YF	PR	Ill Miseq					Ill Hiseq		Ro
Unclassified							<			
Alpha-proteobacteria, Bradyrhizobiaceae, unspec										<

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OTU 469 (o1=one OTU)									>	
Gamma-Proteobacteria, Enterobacteriaceae, Unspec		<				<				
Gamma-Proteobacteria, Enterobacteriaceae, Escherichia/Shigella						<				
Gamma-Proteobacteria, Enterobacteriaceae, Proteus						<				
Gamma-Proteobacteria, Moraxellaceae, Unspec						<				
Gamma-Proteobacteria, Moraxellaceae, Acinetobacter						<				
Gamma-Proteobacteria,, Pasteurellaceae, unspec.				>						

Table 6. This table shows the significant relative changes in Firmicute phyla between PD patients (PD) and healthy controls (HC), that were assessed by the ten summarized Parkinson's disease studies.
> symbolizes a higher abundance in HC when compared to PD
< symbolizes a lower abundance in HC when compared to PD
- equals, that no significant change in PD compared to HC was found with the chosen methodological approach.
o1, 2, 3 symbolize, that one, two, three OTU's of the taxa were significantly changed in PD compared to HC
+ indicates that a change in PD compared to HC on the genus and on the species level was found. The methods used by the studies are Yakult Intestinal Flora-SCAN (YF), 96-well block of the ABI PRISM 7900HT Sequence Detection System (PR), Illumina Miseq sequencing (Ill Miseq), Illumina Hiseq sequencing (Ill Hiseq), Roche 454 GS FLX Titanium sequencing (Ro).

4. Discussion

Our data show that the reproducibility of data is very low at the higher taxonomic rank, the phylum level. The inconsistency of the data could indicate, that the changes of the phyla, are facultative, but not obligatory for the NDs. Moreover, it implies, that it is sufficient for an effect on the host, that lower taxonomic levels are altered without achieving an alteration at phylum level. Profound changes of one family could be compensated by oppositional changes in other families of that phylum. In conclusion, comparisons on phylum level are too rough and higher taxonomic resolution is needed to discover similarities of the microbiota composition relating to the diseases.

A negative correlation between PD disease duration and Firmicutes abundance was reported [30]. Additionally, an inverse correlation between the COMT-inhibitor type of PD medication with Entacapone, and Firmicutes abundances was found [35]. These findings show that there is more to PD than a lower Firmicutes phylum abundance, since otherwise Entacapone would not display its beneficial effects. No other study apart from Keshavarzian et al, 2015, found a significant change in abundance of Firmicute phylum in PD. This implicates the importance of controlling disease medication and disease duration of the subjects during the study since both alter the gut microbiota composition. For the aim of proving a causality, a reduction of confounding may be achieved by enrolling a study population consisting of PD patients at an early stage or/ prodromal stage and no medication.

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Since with progression of age the Firmicutes:Bacteroidetes ratio is found to change [36], an association with neurodegeneration could be considered. However, no study reported any significant differences in Firmicutes:Bacteroidetes ratio in PD. A minority of studies in other NDs, namely two ALS studies [37,38] and one MSA study [39], discovered an aberrant Firmicutes:Bacteroides ratio, indicating no predominant role for the NDs. Moreover, several other factors influence the Firmicutes:Bacteroides ratio. The characteristics of the recruited cohort are crucial. In elderly but also in infants, the ratio is extremely low [36]. It was suggested that the Firmicutes:Bacteroidetes ratio is also associated with obesity [40-43], but a causative key role for this ratio for obesity was questioned by other groups [44]. Different types of diet change the Firmicutes to Bacteroides ratio [45] and it was reported that the freezing process of faecal samples before extracting the DNA, significantly increases the Firmicutes:Bacteroides ratio [46]. Other methodical choices, like choosing between the different bead-beating cell lysis instruments before metagenome analysis influence this ratio up to threefold in favour of Bacteroides [47]. Taken together, these data indicate, that the shift is not specific for neurodegenerative diseases and might sometimes be a consequence of technical and lifestyle factors.

Several alterations in the Firmicutes phylum were reported in PD and other NDs. Commensal *Clostridium species*, like *Clostridium saccharolyticum* and *Clostridium leptum*, showed a significant and descriptive decrease in PD [34]. This reduction is in agreement with the observed reduction of the genus *Clostridium* in AD [48] and MS [49]. By contrast, an increase of the harmful species *Clostridium perfringens* was shown by one study in NMO patients [50]. This is a very interesting finding, since NMO is a demyelinating disease that is associated with antibodies against the water channel protein aquaporin-4 (AQP4) expressed on astrocytes and T helper 17 cells [51]. These antibodies are reported to exhibit a cross-reactivity to a homologous peptide sequence within adenosine triphosphate-binding cassette (ABC) transporter permease of *Clostridium perfringens* [51,52]. Also, a theoretical involvement of the epsilon-toxin of *Clostridium perfringens* in inducing neurodegeneration was proposed in MS, due to its ability to cross the blood-brain-barrier, damaging oligodendrocytes and due to its observed contribution to enterotoxaemia in ruminants [53-55]. However, no increased *Clostridium perfringens* was found in the five MS studies [49,56-59]. Nonetheless, epsilon toxin might play a role in NMO, since it can damage optic nerves in vivo [60]. This and the possibility to vaccinate against epsilon-toxin, at least in rodents, point to an importance of the observed increase of *Clostridium perfringens* in NMO [61] .

Lactobacillus was increased in three of ten PD studies, in contrast to AD [48], MSA [39,62], ALS [37,38,63] and NMO [50], where no change was observed. However, this increase of *Lactobacillus* in PD patients could be caused by the frequent constipation of PD patients, since *Lactobacillus* is also known to be increased in the constipation-type of IBS and decreased in the diarrhoea-type of IBS [64] and the co-variable constipation was methodically and statistically treated differently in the PD studies. The decrease of both *Lactobacillus* and *Lactobacillus rogosae* that was reported in MS patients [49,58] supports the above hypothesis, since several medications against MS lead to diarrhoea [65,66]. The possibility that a probiotic intervention or preventive treatment with beneficial *Lactobacillus* strains could have an ameliorating effect on MS deserves to be investigated.

Increased Lactobacillaceae abundance and decreased *Prevotella* has been linked to reduced ghrelin concentration and altered ghrelin secretion has been reported in one PD study [35]. Ghrelin is a gut hormone that may contribute to the maintenance and protection of normal nigrostriatal dopamine function [67]. Future studies should investigate, if *Lactobacillus* has a constipation-related consecutive role, or rather a causative role. Such studies could, moreover, define which *Lactobacillus* species are beneficial, and which may be detrimental. This differentiation is essential, since there are probiotic treatment proposals for PD which include *Lactobacillus* strains and on the other hand the potential harmful link to reduced ghrelin secretion has not been sufficiently investigated.

Two PD studies showed an increase of Ruminococcaceae family [23,27], which might also discriminate PD from other NDs, since in other NDs either no change or even a decrease was observed, namely in AD [48], MSA [39], MS [68] and ALS [38]. The increased Ruminococcaceae on

family level might play a role in PD patients, however, which subordinate taxa contribute to the disease cannot be unequivocally stated yet.

Faecalibacterium partly specified as *Faecalibacterium prausnitzi* or as an OTU showed a significant decrease in four PD studies [26,27,29,35] while this was not observed in any other ND apart from MS [49,57]. In ALS an increase was noted in one study [69]. However, *Faecalibacterium* showed a negative correlation to Entacapone taxa [35] and a positive correlation to vitamin D supplementation in MS patients [57], indicating that also other factors might contribute to the observed change of *Faecalibacterium* abundance. Thus, the specific *Faecalibacterium* change in PD might be provoked by extrinsic factors including medication or nutrition. Nevertheless, *Faecalibacterium prausnitzi* is advocated as a potential future probiotic due to some strain-dependent anti-inflammatory features, like butyrate-production [70]. However, the hypothesized beneficial effects on intestinal barrier integrity resulting in anti-inflammatory benefits could not be confirmed by one study in an *in vitro* model of the large intestine [71]. Since the *Faecalibacterium prausnitzi* species include a high diversity of strains, a strain-dependent classification and investigation would improve the insight of beneficial and harmful effects on the host [72].

Lachnospiraceae family showed a depletion not only in PD [27], but also in MSA [39], MS [68] and ALS [37]. Even if this reduction on family level is not specific to PD, it is still interesting, because Lachnospiraceae include many putative anti-inflammatory, and thus potentially protective genera. In addition, Lachnospiraceae were negatively correlated to disease duration in PD patients [30]. Thus, this reduction might just be a consequence of common disease-related changes. The key members of Lachnospiraceae showed a confirmed decrease in PD (Table 2). Interestingly *Blautia* and *Dorea* are also decreased in MSA [39], while AD [48], NMO [50] and MS [58] showed an increase of *Blautia* and MS [58] and ALS [37] a decrease of *Dorea*. On family level the decrease of Lachnospiraceae is correlated with PD disease duration and the abundance of Lachnospiraceae might be, like the incidence of PD, sex-dependent [28]. Concluding that the decrease of *Blautia* and *Dorea* in case-control-studies is limited to alpha-synucleinopathies like PD and MSA, it is tempting to investigate, if these genera additionally correlate with longitudinal data of PD and MSA patients and if the changes predate the neurodegenerative progress and symptoms.

Another family, Christensenellaceae, showed an increase on family and species level, e.g. *Christensenella minuta*, during the course of PD [26,27], a change, which was also observed by one study on genus level of *Christensenella* in MS patients [68]. Thus, these changes might not be specific but still characteristic for some PD patients. Same applies to the increase of *Oscillospira* in PD [26,30]. Petrov, et al, moreover, explained recently that Christensenellaceae is a heritable taxon and that it is co-abundant with *Oscillospira*. These taxa are, like PD, significantly associated with lower body weight [73], which might indicate a higher vulnerability for PD, or more severe PD stages, when these families were inherited.

Two different species of *Eubacterium* were observed to be decreased in PD, MS and a case-control-study of a cognitive impaired elderly without an explicit AD diagnosis [31,49,74]. In the cognitive impaired elderly, a negative correlation between *E. rectale* and proinflammatory cytokines IL-1b, NLRP3 and CXCL in addition to a positive correlation between these cytokines and *Escherichia/Shigella* was observed [74]. This might imply an anti-inflammatory role for several Eubacteria species in the development of neurodegenerative diseases. Regarding changes in the metabolome of colonic microbiota, *Eubacterium* contributed the most to the decrease in genes for D-glucuronate degrading enzymes and two more active tryptophan metabolism pathways observed in PD patients [31]. Glucuronidase enzymes mediate the regeneration of molecules important for host health, but also toxins and carcinogens [75]. Moreover, they activate endogenous glucuronides of hormones and neurotransmitters [75]. L-Tryptophan is the precursor of serotonin and is shown to be decreased in PD patient brains [31] and its metabolites display regulatory immune function with beneficial and harmful potential . Finally, some non-significant trends, between Unified Parkinson's disease rating scale III (UPDRS III) and abundances of e.g. *Eubacterium rectale, Eubacterium. hallii* and *Eubacterium eligens* were reported [31]. This is mentionable since *E. rectale* might penetrate the mucus

layer due to its flagella. Interactions between *E. rectale*, the mucus layer and the intestinal mucosa are therefore feasible.

The members of the phylum of cyanobacteria, which belong to the blue-green algae, produce a series of neurotoxins, from which beta-N-Methylamino-L-alanine (BMAA) is the most common. However, the production of neurotoxins by their candidate phylum sibling Melainabacteria is not yet well investigated [76]. A link between cyanobacterial derived neurotoxins and neurodegenerative diseases was shown already more than ten years ago by Cox et al, who examined the Chamorro people of Guam, who exhibit a 50-100 times higher incidence of ALS than anywhere else [77]. BMAA is linked with intraneuronal protein misfolding, which is an important pathological hallmark of many NDs. High levels of neurotoxin BMAA has been associated with AD [78]. Post-mortem brain specimens of ALS, AD and Huntington disease (HD) patients showed increased BMAA concentrations [79]. Moreover, BMAA targets N-Methyl-D-aspartate (NMDA) receptors and the neurotransmitter glutamate, which are believed to be disturbed in AD. Also, other cyanobacterial derived neurotoxins could play a role in neurodegeneration in individuals with more permeable intestinal epithelial barrier of the GI tract, like the leaky gut observed in elderly people [80]. However, none of the examined studies detected an altered relative abundance in Cyanobacteria in PD. Also, in other neurodegenerative diseases like AD [48], MSA [39,62], MS [49,56-58,68], ALS [37,38,63] and NMO [50], no change in this phylum was reported. Only Heintz-Buschart et al, reported a decrease of an unclassified OTU171 with high resemblance to the Melainabacterium MelB1,57 in PD. However, they could not asses any of the known cyano-neurotoxins [32]. This and the fact that this Melainabacterium was decreased in PD speaks in favour of a protective outcompeting role, possibly by replacing other harmful cyanobacteria. Products of other bacteria, belong to the phylum of red algae, such as a phycoerythrin, were shown to have an ameliorating effect on AD [81,82]. It can be summarized that Cyanobacteria can produce neurotoxins that lead to neurodegeneration, but the abundance of Cyanobacteria is only increased in special, sometimes isolated populations. The role of the newly detected phylum of Melainabacteria is not yet clear, but so far, no harmful association could be found and even a protective role can be postulated.

Only few changes were reported in the phylum of Actinobacteria, but these were consistent regarding several taxonomic resolutions (Table 3). PD patients showed an increase on phylum level [29], that was reflected in an increase in Bifidobacteriaceae (family) [27] and *Bifidobacterium* (genus) [26,27,35], while no changes were observed in any other examined NDs. In contrast, AD patients showed a decrease on phylum level, reflected by a decrease in Bifidobacteriaceae (family) and *Bifidobacterium* (genus) [48]. Despite the findings of an increased Bifidobacteriaceae in PD, a two-year follow-up study showed that a decrease in *Bifidobacterium* later in disease may be able to predict whether PD stage is going to deteriorate or not, even correlating with the Unified Parkinson's disease rating scale I (UPDRS I) score [83]. This implicates that the increase in Bifidobacteriaceae in PD is not detrimental to the patients, but this rather may represent a mechanism of beneficial action against neurodegenerative aggravation. Thus, it may be postulated that a probiotic intervention with *Bifidobacterium* could prevent progression of PD to severer stages.

Within the phylum of Bacteroidetes *Prevotella* is a well-known and often discussed genus. However, changes in PD patients were not consistent throughout the PD studies (Table 4). In one study, which failed to find any significant difference in relative *Prevotella* abundance between PD subjects and controls, *Prevotella* still was the most reduced bacterium and differed 3.2-fold [34]. In another study without statistically significant change of *Prevotella*, an association between the family Prevotellaceae and the clinical score of PD severity, the UPDRS-III score, was reported [33]. Moreover, trends showing a decrease in *Prevotella* were obtained by one study, when looking at the microbiome of colonic mucosa, rather than faeces [30]. Negative results concerning significant changes in *Prevotella* could be a consequence of methodological differences and other criteria for control subjects [30]. The fact that Prevotellaceae was decreased in idiopathic rapid eye movement

behavioural sleep disorder, iRBD, which predates PD in the majority of cases, supports the hypothesis that this family and its genus *Prevotella* might only be changed in early stages of PD. It is also suggestive, that a decrease of *Prevotella* contributes to the onset of PD and therefore could be used as a biomarker for PD diagnosis [32]. However, unambiguous interpretation of changes of *Prevotella* is difficult, since their abundance also depends on social factors, as observed in monkeys [84] and subgenus differences in *Prevotella* and *Bacteroides* have been related to different dietary patterns [85].

Additionally, the change in abundance of *Prevotella* depends on the species type (Table 4). *Prevotella copri* and *P. clara* were decreased in PD [26,31,49]. This reduction is in agreement with reduced abundances in MSA [62], MS [56] and NMO [50]. In contrast, the species *Prevotella melaninogenica* and one OTU of *Prevotella* showed an increase in PD [31] and NMO [50]. *Prevotella* exhibited one of the highest effect sizes of change in the study of NMO [50]. The fact that certain *Prevotella* species (especially *Prevotella copri*) indeed are decreased in all NDs, apart from AD (see table A1. in the Appendix Section A), suggests a possible protective role against neurodegenerative processes in the brain and therefore deserves future investigation.

In the Verrucomicrobia phylum, four studies found *Akkermansia* genus or species increased in PD patients [27,30-32]. Moreover, both high colonic Akkermansia abundance and PD were shown to negatively be correlated to the BMI [86]. *Akkermansia muciniphila* exerts beneficial effect on the intestinal mucosal layer and improves the barrier function of gut epithelium [31]. Thus, in conditions of low *Akkermansia* abundance, the maintenance of a healthy gut barrier may be not possible anymore, and pathogenic factors of other bacteria, like Lipopolysaccharide (LPS), could consequently harm the host. On the other hand, *Akkermansia* uses mucus as an energy source and degrades the mucus layer [87]. This could lead to an increased exposure of microbial antigens to immune cells and thus could have an inflammatory potential. The role of the pro- and anti-inflammatory properties is not yet clear but maintaining a steady state of *Akkermansia* may be a pre-requisite for normal functioning of the gut homeostasis. *Akkermansia* together with *Eubacterium*, *Capnocytophaga*, *Phascolarctobacterium* and OTUs no further classified than to Firmicutes, achieved a high prediction score for PD [31].

No changes within the phylum of Proteobacteria, apart from the family Enterobacteriaceae [29,35] were reported in PD patients. Therefore, it can be concluded that the relative abundance of these taxa is only changed in a minority of patients. Because of the missing confirmation of these alterations, the clinical relevance of these findings can be questioned. *Escherichia coli*, a member of Enterobacteriaceae family, showed translocation into the colonic mucosa in PD patients [88]. The complexity of this interrelationship is shown by the increased abundance of Enterobacteriaceae in PD patients with the postural instability and gait difficulty (PIGD) phenotype compared to the tremor-dominant subtypes (TD) [33]. The more progressive and severe pathology of non-TD-phenotypes (including PIGD) supports the idea of a different unknown pathological mechanisms underlying this subgroup of PD [33]. The observed difference in Enterobacteriaceae abundance between the subgroups of PD disease might equally occur due to other variable phenotype features in this study: PIGD subjects tended to be older and to have higher nonmotor symptoms scale (NMSS) total scores than TD subjects [33]. These differential abundant taxa between PD phenotypes was challenged by another study [35] as these researchers only found an overall increase in PD [29,35]. However, in this study Unger et al, used a slightly different classification and they interpreted their results based on a small number of the TD patients in their sample. In agreement to the findings in PD, also a significant increase of Enterobacteriaceae and some other taxa of Proteobacteria phylum was observed in NMO. The mentioned change in Enterobacteriaceae was not only significant but they were also four times higher abundant than in healthy controls [50]. A protective role of Enterobacteriaceae was proposed by Hasegawa et al, demonstrating that Enterobacteriaceae (and *C. perfringens*, *B. fragilis*, and *Pseudomonas*) produce hydrogen water (1000ml/d) and were associated with improved total UPDRS scores in PD patients in a double-blind randomized controls study [89]. In addition, they were shown to be protective against PD pathology in rats [90]. These researches performed a study to access,

whether the total amount of breath hydrogen in PD patients was lower than those in healthy controls and confirmed this hypothesis [34]. The results regarding the potential protective or aggravating role of Enterobacteriaceae are contradictory to date and need further investigation.

A high number of microbiota composition changes found in human case-control studies of ND concern unclassified bacteria. Approximately 40% of the gut microbiome cannot be captured by reference-genome-based methods [91]. It is hypothesized that during ND unclassified bacteria gain more importance. Heintz-Buschart et al, discovered 10 depleted unclassified OTUs in PD patients that exhibited together very low fractional abundance [32], but they still could manipulate host's health via an unknown unique mechanism without a need of high abundance. Interestingly, the genome of OTU 469, encoded an endoglucanase with a synuclein-like domain and thus may lead to an immune system that is tolerant to alpha-synuclein like structures [32]. This could have a potential implication for induction of PD and MSA pathology. The depletion of this bacterium leads to a lack of host's immune system exposure to the bacterial alpha synuclein like structures, which may result in an immunologically induced alpha-synuclein-aggregation. This hypothesis is in line with the reports, that alpha-synuclein aggregation starts in the enteric nervous system and not in the brain [1,3,92]. All unclassified OTUs of this study, where the genome could be recovered, showed common features such as fermentative lifestyle, motility and the ability to synthesize vitamins. The great number of observed changes in unclassified Bacteria or single OTUs must be handled carefully, since the method of quantification of the most included studies was 16S rRNA amplification and high-throughput sequencing, which is known to prone to sequencing errors and chimera creation, leading to an artificial high diversity and low reproducibility [93]. Lastly, no studies analysed the gut microbiome of iRBD patients yet (apart from Heintz-Buschart et al, 2017), but this disease showed a high conversion rate to alpha Synuclein disorders, especially PD. More investigations of microbiome in prodromal stages of diseases with follow up evaluation are necessary.

Only one human case-control study analysed the colonic microbiome of AD patients [48]. Most AD patients were in the stage of mild or very mild AD according to clinical dementia rating (CDR) scores. Targeting the early stage of the AD may help to examine possible causal associations between microbiome compositional changes and the disease onset. Limited overlap was found between changes of the microbiome in AD and changes identified in any of the ten PD studies. Minor similarities were observed that included a decreased Firmicutes phylum and Clostridium genus in AD, whereas an almost significantly decreased Clostridium leptum [34] or significant decreased Clostridium saccharolyticum [31,34] was observed on PD. Moreover, AD showed an increased Bacteroidetes phylum, *Bacteroides* genus [30] and Alistipes genus, while increased Alistipes shahii [31] was evident in PD patients. As the above findings were only found in a minority of the cohorts, no great similarity between the microbiome of AD and PD can be concluded so far.

5. Conclusions

Changes in composition of colonic microbiota are found in PD and several other NDs. Some evidence emerges, that assessing the microbiota composition at high taxonomic resolution, can lead to specific alterations in relative abundance for one disease or disease group that might evolve discriminative power. For example, decreased *Blautia* and *Dorea* is limited to alpha synucleinopathies like PD [26,27,29,30] and MSA [39]. Inheriting increased Christensenellaceae and co-abundant increased *Oscillospira*, might predispose for a higher vulnerability for PD or more severe PD stages [26,30] and *Prevotella* reduction occurs in early PD stages and might function as biomarker for PD [32]. A definitive concluding rating of the importance of these changes for the development and diagnosis of NTs, however, is difficult to date. The reasons lay in methodological discrepancies collecting and analysing the microbiome as well as varying sample and effect sizes. Moreover, other confounders such as genetics, medication, nutrition and life style factors may result in obtaining insignificant or falsified results. Therefore, methodical standardization is necessary for ensuring the collection of comparable, reliable and reproducible data. To compare microbiota composition between studies and diseases, it is most straight-forward to first assess the known microbiota via the

more reliable microarray methods and additionally make a functional analysis. In a next step, one may try to detect new species via 16S rRNA sequencing. Finally, the functional variability within one species and the change of features due to plasmid exchange deserves more attention. The interactions between bacterial species and strains and moreover the co-abundances must be more deeply investigated before assumptions on effects of specific bacteria on the host can be made.

Acknowledgments: We thank Prof. D. Wolfer for critically reading this manuscript.

Author Contributions: MHM and SG developed the idea, made the literature search and edited this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

A1. Changes in relative abundances in neurodegenerative diseases

Phylum and family	Genus (species, OTU)	AD	PD	MSA	NMO	MS	ALS	Reference
Unclassified bacteria								PD: [31]
Firmicutes								
Unspecified								AD: [48], PD: [30], MSA: [39], ALS: [37]
unclassified								PD: [31], NMO: [50]
								NMO: [50]
91otu15265	o1 = one OTU							NMO, o1: [50]
Lactobacillaceae	Unspec.							PD: [33], [27], [28]
								PD: [35]
	Lactobacillus (m = mucosae, g= gasseri, c= casei, f = fermentum, re=reuteri, ru=ruminis), r=rogosae		+			+		PD:, [27] +m: [26], +g, c, f, re, ru: [34], MS: [58], r: [49]
Enterococcaceae	Unspec.							PD: [28], [29]
								PD: [35]
	Enterococcus							PD : [29]
Ruminococcaceae	Unspecified O1 = one OTU		+					AD: (Vogt et al., 2017) PD:, o1: [27], [33] MSA : [39], MS: [68] ALS: [38]
	unclassified						*	PD: [27], NMO: [50], ALS: [63] detected differences in certain unculturable Ruminococcaceae in ALS patients but didn't describe the scale and direction.
	Ruminococcus b =bromii		+					PD, b: [26], NMO: [50], MS, o38 : [57]

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	c =callidus o38 = 38 OTUs		+					PD: [29], c: [26] ALS: [38]
	Papillibacter cinnamivorans							PD: [26]
	Faecalibacterium *p = prausnitzi* o2= two OTU o57 = 57 OTU		+			+		PD: +o2: [27] [26], [29], p [35] MS, +p: [49], o57: [57]. ALS: [37]
Lachnospiraceae	Unspec.							PD: [27], MSA: [39] MS: [59], ALS: [37],
	Unclassified o3= three OTU		+		+			PD, o3: [27], NMO, o1: [50]
	Lachnospira,							ALS: [37]
	Roseburia o2=two OTU		+					PD: [30], +o2: [27], MS: [49]
	Coprococcus, e= eutactus o1 = one OTU		+					PD: [30], e:[26], o1: [27], NMO: [50]
	Blautia, g = glucerasea p= producta o1= one OTU		+		+			AD : [48]PD: [30], [29] +o1: [27], g:[26], MSA: [39] NMO, p,o1: [50], MS: [58]
	Dorea,, l=longicatea		+					PD: +l [26], MSA :[39], MS: [58] ALS: [37]
	Anaerostipes, h= hadrus					+		MS, +h: [49], ALS: [37]
Catabacteriaceae	*Catabacter h= honkogenesis*		+					PD, +h : [26]
Clostridiaceae	Unspec.							AD : [48] MSA: [39]
	SMB53							AD: [48]
	Anaerotruncus							PD: [32]
	Clostridium, *p = perfringens* *s =saccharolyticum,*		+		+			AD : [48], PD, s: [34], [31], NMO, p: [50], MS : [49]
Eubacteriaceae	*Eubacterium, r= rectale, b = biforme*		+ *			+		PD, +b: [31] *classified as Erysipelotrichoceae in original publication, MS, r : [49],
	[Candidatus Stoquefichus massiliensis]							PD: [26]
Erysipelotrichaceae	*Unspec.*							PD : [29]
	cc115							AD: [48]
Christensenellaceae	unspecified							PD: [27]
	unclassified							PD: [27]
	Christensenella, m=minuta		+					PD, +m: [26], MS: [59]
Gemellaceae	*Unspec*							AD: [48]
	Gemella							AD: [48]
Mogibacteriaceae	*Unspec.*							AD: [48]
Oscillospiraceae	*Oscillospira*							PD: [26], [30],
	Oscillobacter							ALS: [37]

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Streptococcaceae	*Unspec.*							PD : [29]
	Streptococcus t/s= thermophilus/salivarius					+		PD : [29], MS, t/s : [49]
Peptococcus	*Desulfotomaculum sp. CYP1*							MS: [49]
Peptostreptococcaceae	*Unspec.*							AD: [48]
Acidaminococcaceae	*Phascolarctobacterium*							AD: [48]
	Acidaminococcus							PD : [29]
Veillonellaceae	*Unspec.*							PD : [29]
	Megamonas, f= funiformis							PD : [29],
	YIT11815					+		MS, f: [49]
	Megasphera							PD : [29]
	Dialister							AD: [48]
Tissierellaceae	*Tissierella*							PD: [27]
Turicibacteraceae	*unspec.*							AD: [48]
	Turicibacter							AD: [48]
Tenericutes								
Unclassified								NMO: [50]
Acholeplasmataceae	*Acholeplasma*							NMO: [50]
	[Candidatus Phytoplasma]							NMO: [50]
Melainabacteria								
OTU_171 (98.9% identity to MelB1,57)								PD, o1: [32]
Actinobacteria								
Unspec.								AD: [48], PD : [29], MS : [59]
Bifidobacteriaceae	Unspec.							AD: [48], PD: [27]
	Bifidobacterium							AD: [48], PD: [26], [27], [35], MS: [59]
Coriobacteraceae	*Unspec.*							PD : [29]
	Adlercreutzia							AD: [48], MS: [58]
	Collinsella							MS: [58], [56]
	Slackia							MS: [56]
	Eggerthella lenta							MS: [49]
Corynebacteriaceae	*Corynebacterium*							NMO: [50]
Fibrobacters								
unclassified								NMO: [50]
Gemmatimonades								
91otu1 0683	o1= one OTU							NMO, o1: [50]
Bacteroidetes								
Unspec.								AD: [48] PD: [30] MSA: [39], ALS: [37]
								PD: [35], [29]
unclassified								NMO: [50]
Bacteroidaceae	Unspec.					+		AD: [48]

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	o37= 37 OTUs						MS, o37: [57]
	Bacteroides f=fragilis, m=massiliensis, cc=coprocola,, cp= coprophilus, d=dorei, p=phlebeus, s=stercoris			+			AD: [48], PD: [30], MSA, f :[62], NMO: [50], MS : [59]
			+				PD, +m, c, d, p: [26], f : [34], MS, s, cc, cp: [49], ALS : [37]
Flavobacteriaceae	*Flavobacterium*						NMO: [50]
Prevotellaceae	Unspec						PD: [33]
	Prevotella, co =copri, cl=clara, M= melaninogenica o1= one OUT, o2= two OTU		+	+	+	+	PD,+ co : [31], [26] MSA, cl: [62] NMO, co, o2: [50] MS, +co : [49], [56], ALS: [37]
			+		+		PD, o1: [27] NMO, m: [50]
Porphyromonadaceae	Unspec.						MSA: [39],
	Unclass.						NMO: [50]
	Parabacteroides						MS: [58]
							PD: [27], MS: [59]
	Barnesiella						PD: [28]
	Butyricimonas						MS: [56]
Rikenellaceae	Unspec						AD : [48], MSA : [39]
	Alistipes, s=shahii		+				AD : [48], PD, s : [31]
Sphingobacteriaceae	*Pedobacter*						MS: [58]
Elusimicrobia							
91otu12128	o1 =one OTU						NMO, o1: [50]
Plantomycetes							
unclassified							NMO: [50]
Verrucomicrobia							
Unspec							PD: [32], MS: [56]
Verrucomicrobiaceae	Unspec.						PD: [27] [33] [30] [32]
Akkermansiaceae	*Akkermansia, m=muciplila*		+				PD: [27], [30], +m: [31] [32], MS: [56], [59]
[Chthoniobacteraceae]	DA101 =one OTU						NMO, o1: [50]
Acidobacteria							
91oto412	One OTU						NMO, o1: [50]
Spirochaetes							
Spirochaetaceae	*Treponema socranskii*						NMO: [50]
Proteobacteria							
unclassified							PD: [30], [29]

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Alpha-Proteobacteria								
Unclassified								NMO: [50]
Bradyrhizobiaceae	*unspec*							PD: [33]
Brucellaceae	*Mycoplana*							MS: [58]
OTU_469, o1=one OTU								PD, o1: [32]
Beta-Proteobacteria								
Sutterellaceae	*Sutterella, w= wadsworthensis*					+		MS, w: [49]
Burkholderiacea	*Ralstonia*							MSA: [39]
Oxalobacteraceae	Unspec.							MSA: [39]
Gamma-Proteobacteria								
Unclassified								NMO: [50]
Chromatiaceae	o1 = one OTU.							NMO, o1: [50]
Coxiellaceae	o1 = one OTU							NMO, o1: [50]
Enterobacteriaceae	Unspec.							PD: [35], [29]
	Unclassified							NMO: [50]
	Escherichia							ALS: [37]
	Escherichia/Shigella							PD : [29]
	Proteus							PD : [29]
Moraxellaceae	Unpec.							PD : [29]
	Acinetobacter							PD : [29]
Pasteurellaceae	Unspec.							PD: [27]
Pseudomonadacea e	Pseudomonas							MS: [58]
Delta-Proteobacteria								
Desulfovibrionace	*Bilophila*							AD: [48]
ae	*Desulfovibrio*							MS: [59]
KSB3								
unclassified								NMO: [50]
91otu6419	97otu28635 = one OTU							NMO, o1: [50]

Table A1 Legend

AD: Alzheimer disease
PD: Parkinson disease
MSA: Multiple sclerosis
NMO: neuromyelitis optica
MS: Multiple sclerosis
ALS: amyotrophic lateral sclerosis
o1,2,3, symbolise, that the change is concerning one, two, three or more operational taxonomic units (OTUs)
letter = abbreviation for the species in which the change was observed
Small letters followed by a + indicate, that the change was observed for genus and species
Changes in relative abundance compared to the control, are marked colour coded.
Green: Higher abundance in disease condition.
Orange: Lower abundance in disease condition.
Uncoloured: No study detected a significant change in abundance
- equals, that no significant change in PD compared to HC was found with the chosen methodological approach.

There are three intensity nuances for each colour to show how many of the included study found the same difference and direction.
Light: 1 study
Middle: 2 studies
Dark: 3 or more studies

Coloured fields containing a + indicates, that detailed information concerning species type is found in the other columns

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Peer-reviewed version available at Nutrients 2018, 10, 708; doi:10.3390/nu10060708

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