Universidade do Minho
Escola de Medicina

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Multisensory integration of postural control in Neurodegenerative diseases

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Tese de Doutoramento em Medicina

Trabalho efetuado sob a orientação do
Professor Doutor Nuno Sousa
e da
Professora Estela Bicho

setembro de 2017

STATEMENT OF INTEGRITY

I declare that I have acted with integrity in the elaboration of the present thesis. I confirm that in all the work leading to its elaboration I did not resort to the practice of plagiarism or any form of falsification of results.

I further declare that I have been fully aware of the Code of Ethical Conduct of the University of Minho.

University of Minho, 07 of September of 2017

Nome: Miguel Albino Silva Fernandes do Gago

Signature: 

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ABSTRACT

Introduction: Postural control, results from the dynamic and continuous integration of multiple systems (somatosensory, vestibular, visual, and auditory) in response to the surrounding environment, intrinsic motor condition, cognition and behavioural. Slowed reaction times, delayed information processing and/or inappropriate multisensory integration may explain higher postural instability in Alzheimer's disease (AD) and Parkinson's disease (PD). Albeit levodopa remains the most effective treatment of PD, its effect on postural control remains unclear, even less in Vascular Parkinson's Disease (VPD). **Objective:** Herein, we aimed to study the role of the visual, somatosensory and auditory systems in postural control, and identify postural associated to increased risk of falls and/or specific neurodegenerative diseases. We seek to comprehend the role of muscle tone and levodopa on postural control in PD and VPD, and get insight of dopaminergic and non-dopaminergic networks. Finally, comprehend the compensatory postural adjustments (CPA) to external perturbations in AD and IPD, and clarify the neurophysiological electrical activity coming from different network loops (mechanical vs. cognitive). **Methods:** We developed technological apparatus, hardware and software, using kinematic wearable sensors and virtual reality (VR), as to implement different sensorial paradigms in AD, PD and VPD patients and healthy subjects. Under manipulation of different senses (visual suppression, auditory suppression, inclined platform, and incongruent visual-somatosensory inputs), we studied multisensory integration and reweighting in final postural control, as well as intensity of CPA (different bands of frequency) upon external perturbations. Levodopa challenge was performed in PD and VPD in order to determine the weight of musculoskeletal rigidity on postural control. **Results:** Visual suppression had a negative impact on postural stability, in contrast to the benefit obtained by suppressing background noise. The auditory system proved to have an important role in postural control, by providing spatial cues, and can be a potential factor of distraction. AD fallers and VPD patients presented an increased vulnerability to visual suppression. In early stages of PD, without overt clinical postural instability, postural control is still modulated by levodopa, in contrast to axial rigidity in VPD. In VR, the visual-somatosensory perturbation paradigm elicited different patterns of CPA. AD patients presented delayed CPA, and AD fallers had higher vulnerability to external perturbations (increased power in the LB of CPA). Levodopa, in PD, by reducing muscular stiffness and body restrains, lowered the power of CPA in the HB and strain on cognitive resources. **Conclusion:** Our results give further support to the conceptual model in which postural control results from the multisensorial integration, where different sensory inputs are dynamically and continuously reweighted. In AD, postural instability is due to delayed processing of information, unleashing self-perpetuating erroneous postural adjustments. In PD, rigidity and hypokinesia are the main culprits of postural instability. Without the added benefit of levodopa, PD patients impose a detrimental strain on cognitive resources. In VPD, strategic and/or cumulative cerebrovascular lesion on non-dopaminergic networks, may explain the inferior response to levodopa of the muscle tone in axial limbs and worse postural stability. Quantitative postural analysis opens new venues in a neurophysiological approach of postural control in clinical practice (e.g. differential diagnosis, disease progression and red flags of falls), and as an additional outcome tool in pharmacological and non-pharmacological interventions. VR, complemented by postural analysis, allowing to manipulate and/or mimic daily life ecological paradigms, has the potential to be used in cognitive, motor and behaviour rehabilitation interventions, addressing issues such as learning by trial and error, filtering and susceptibility to irrelevant and intrusive sensorial information, and analysis of the fear factor in inhibitory and compensatory postural responses. Future research, combining different techniques, neuroimaging and postural analysis, as well as mechanistic animal models with strategic vascular lesions, may tackle some of the open questions.

RESUMO

Introdução: O controlo postural resulta da integração dinâmica e contínua de múltiplos sistemas (somatossensorial, vestibular, visual e auditivo), em resposta ao ambiente envolvente e condição intrínseca motora, cognitiva e comportamental. Atrasos na resposta e processamento da informação e/ou inadequada integração multissensorial, poderão explicar maior instabilidade postural na Demência de Alzheimer (DA) e na Doença de Parkinson (DP). Embora a levodopa continue a ser o tratamento de eleição na DP, permanece incerto o seu efeito no controlo postural, e menos claro ainda na doença de Parkinson Vascular (DPV). **Objetivo:** Compreender o contributo de diferentes sistemas (visual, somatossensorial e auditivo) no controlo postural, bem como identificar perfis posturais associados a um maior risco de queda e/ou específicos de doença neurodegenerativa. Pretendemos determinar o papel dos tônus muscular e da levodopa no controlo postural na DP e na DPV. Finalmente, compreender os ajustes posturais compensatórios (APC) em reação a perturbações externas, na DA e na DP, e destrinçar a atividade neurofisiológica intrínseca de diferentes circuitos neurais (mecânico versus cognitivo). **Métodos:** Foi desenvolvido aparato tecnológico, *hardware* e *software,* com recurso a sensores cinemáticos e realidade virtual (RV), de forma a serem implementados diferentes paradigmas sensoriais em doentes com DA, DPI e DPV, e controlos saudáveis. Fazendo uso da manipulação sensorial (supressão visual, supressão auditiva, plataforma com inclinação, e incongruência visual-somatossensorial), analisamos a integração e reponderação multisensorial no controlo postural final, bem como a intensidade dos ACP (em diferentes bandas de frequência) perante perturbações externas. A prova da levodopa, em doses supramáximas, foi utilizada para caracterizar a contribuição da rigidez do sistema musculo-esquelético no controlo postural. **Resultados:** A supressão visual teve um impacto negativo na estabilidade postural, contrastando com o benefício obtido com a supressão do ruído de fundo. O sistema auditivo tem um papel importante no controlo postural, ao fornecer pistas de localização espacial, podendo ser um potencial fator de distração. Os doentes com DA e maior risco de quedas, assim como os doentes com DPV, apresentaram maior vulnerabilidade à supressão visual. Nos estádios iniciais da DP, sem instabilidade postural clinicamente objetivável, ainda é possível a modulação dopaminérgica no controlo postural, contrastando com a rigidez axial na DPV. Na RV, o paradigma de perturbação visual-somatossensorial, desencadeou diferentes padrões de ACP. Os doentes com DA apresentaram um atraso no início dos ACP, e os doentes com maior risco de queda, maior susceptibilidade a perturbações externas (maior intensidade do sinal de ACP nas baixas frequências). A levodopa, na DPI, ao reduzir a rigidez muscular e as restrições corporais, diminuiu a intensidade dos APC nas altas frequências, reduzindo a compensação por ativação de recursos cognitivos. **Conclusão:** Os nossos resultados suportam o modelo conceptual em que o controlo postural resulta da integração de diferentes sistemas sensoriais, sendo que o peso de cada sistema é ajustado de forma contínua e dinâmica. Na DA, a instabilidade postural é essencialmente devida a um atraso no processamento da informação, desencadeando ajustes posturais errôneos que se auto perpetuam. Na DP, a rigidez e os hipocinésia são os principais responsáveis pela instabilidade postural. Na ausência do efeito benéfico da levodopa, os doentes colocam os seus recursos cognitivos sobre excessiva pressão compensatória. Na DPV, lesões cerebrovasculares estratégicas e/ou cumulativas em redes não dopaminérgicas, poderão explicar o menor efeito da levodopa no tônus dos músculos axiais. A análise posturográfica abre novas portas a uma progressiva abordagem neurofisiológica e quantitativa do controlo postural na prática clínica, posicionando-se como uma nova ferramenta, quer a nível de diagnóstico (p.ex. diagnóstico diferencial, progressão clínica e risco aumentado de quedas), quer em intervenções farmacológicas e não farmacológicas. A RV, complementada com a análise posturográfica, permitindo a manipulação e/ou replicação de paradigmas ecológicos de vida diária, tem um futuro potencial na reabilitação cognitiva, comportamental e motora, ao abordar questões como a aprendizagem por tentativa e erro, filtragem e susceptibilidade a informação sensorial irrelevante e intrusiva, e análise do fator medo nas respostas inibitórias e compensatórias posturais. Em futuras pesquisas, a combinação de diferentes técnicas de neuroimagem com a análise posturográfica, bem como modelos animais mecanicistas de lesões vasculares estratégicas, poderão igualmente abordar algumas das questões em aberto.

INDEX

ABBREVIATIONS

AD – Alzheimer's Disease

APA - anticipatory postural adjustments

CPA - compensatory postural perturbations

CPG – central pattern generators

COM – center of mass

CNS – Central Nervous System

HB – higher band

IPD- Idiopathic Parkinson's Disease

LB – lower band

MLR - mesencephalic locomotor region

mPIGD – modified Postural Instability and Gait Disorder score

PI – postural instability

PPN - peduculopontine nucleus

VR- virtual reality

VPD – Vascular Parkinson's Disease

CHAPTER 1 – INTRODUCTION AND BACKGROUND CONCEPT

Postural control is a complex mechanism that integrates a continuous stream of information from multiple sensorial systems - including visual, vestibular, somatosensory, auditory systems, and higher level cognitive processes - generating appropriate synergic postural muscle movements of the head, eye, trunk, and limbs [1-4]. This multisensorial integration results from a continuous dynamic self-assessment of postural balance, based on an internal body schema, being critical to sustain the center of mass (COM) of the body, relative to its base of support, within limits of stability[5]. Disruption in any of these systems, central or peripheral, leads to perturbations in postural balance, increasing the risk of falls[6]. With ageing there is progressive deterioration in some of these systems of postural control, such as reduced vision [7], impairment of sensorimotor function and peripheral sensory loss and/or muscle weakness[8], and slowed reaction times in response to perturbations [9], leading to falls. Some of these deficits may explain the higher risk of falls in the elderly but cognitive factors, especially in neurodegenerative diseases, have also to be accounted for as potential variables. Indeed, neurodegenerative disorders, such as Alzheimer's disease (AD) and Idiopathic Parkinson's Disease (IPD), are associated with postural and gait disturbances, increasing the risk of falls [10,11]. The human postural control model is still not fully comprehended, even less comprehended are the underlying mechanisms behind postural instability in neurological diseases. This thesis is centered in the need of more research in postural control in order to implement more effective preventive measures of falls, or guide pharmacological and rehabilitation interventions in neurological diseases. In the reminder of this chapter we do a review of current concepts of the different systems and neural networks involved in postural control (visual, auditory, somatosensory, musculoskeletal and cognitive), as well as open issues in this field, that have underpinned the main objectives and methodology of our research.

1.1. The different systems involved in postural control

Visual System

Visual perception is a critical factor for human postural control, giving cues for body orientation in relation to the surrounding environment, in relation to depth, distance and velocity of objects, under voluntary and involuntary actions[12]. Undoubtedly, vision is the most significant contributor to postural control, playing a bigger role than proprioception, vestibular [12] or auditory systems[13]. Previous studies have shown that upon visual suppression postural control, even though relying and compensating with inputs coming from the vestibular and proprioceptive systems, deteriorates with increasing postural sway [14]. Still, in healthy subjects, it remains unclear how the visual system is reweighted with the remaining senses, especially in

the dynamic conditions of daily living. In AD, it has been shown a detrimental over reliance in visual information, which may explain the higher postural instability and risk of falling[14]. Yet, it is not clear if this is a sole specific deficit of the visual system in AD or, in contrast, a multisystem deficit including slower perception or slower multisensorial integration in postural control. IPD patients exhibit different visual acuity in comparison with healthy subjects, possible due to reduction in retinal dopamine[15]. Also, in experiments using virtual reality (VR), it was found that IPD patients have a degeneration in visual depth and dynamic perception[16]. Still, there is no clear information how this correlates to postural instability in IPD.

Auditory System

Auditory orientation is ensured by binaural cues, which involves central assessment of differences in time and intensity between the auditory inputs coming from the two ears, and by non-binaural cues, which influence postural alignment and the ability to locate sounds[17].In everyday life, audition is important for body self-location in space and distance from objects, being an additional input for normal multisensorial integration of postural control. However, an auditory stimulus can also have a disturbing effect on postural stability. An unpredictable auditory stimulus can challenge postural stability, requiring postural adjustments to recover balance. Previous studies have shown that both a static auditory stimulus, independent of the type of spatial location source of the auditory stimulus[18], or a moving auditory stimulus, can increase body sway[19]. It remains unclear how the auditory system interacts with other systems in postural control in healthy subjects, even less in neurodegenerative diseases, where studies are absent. It is plausible to assume that in neurodegenerative disorders, where central sensorial integration can be compromised, unpredictable auditory stimulus can provoke a detrimental cascade of postural adjustments leading to higher risk of falling. Yet, this assumption deserves further confirmation.

Somatosensory and musculoskeletal systems

The somatosensory system provides perception about external and internal state of the body, including temperature, pain, discriminative and crude touch, visceral sensation, and proprioception. Proprioception is critical for conscious and unconscious modalities of the human movement, providing real time feedback of the status of the musculoskeletal system and position and movement of our different body parts. Proprioception is provided by afferent nerve fibers arising from muscle spindles and Golgi tendon organs in limb joints, that relay in intraspinal arc reflex networks, ipsilateral spinocerebellum and contralateral somatosensory cortex[20].

According to the biomechanics of human movement, the musculoskeletal system (muscles, bones, tendons and ligaments) is its final effector. As so, the status of musculoskeletal system, conveyed by the proprioceptive system, is certainly a non-negligible variable in postural control. It is thus not surprising that, even in individuals without neurological disease, a poor muscle conditioning, lower body mass index, results in worse postural control performance and

increased risk of falls[21]. Increased muscle tone, rigidity, spasticity, dystonia or even paratonia, can have a detrimental effect on postural control. Together with hypokinesia, rigidity is one of the cardinal signs in IPD. Dopaminergic therapy, in particular levodopa, has proven to be effective on improving hypokinesia and limbs rigidity[22]. However, levodopa may not be so effective in improving axial rigidity as limb rigidity [23], which may explain why its role in postural balance remains extremely controversial. In fact, postural sway is unaffected or even worsened by levodopa, where maintenance of balance during standing may worsen due to levodopa-induced dyskinesia[22]. There is increasing evidence that non-dopaminergic structures, such as peduculopontine nucleus (PPN) and mesencephalic locomotor region (MLR) in the brainstem, have a fundamental role in locomotion and postural control [24,25]. These nuclei have predominantly acetylcholine (Ach) receptors, which may explain why levodopa has a lower effect in postural control. Although there is evidence that extrapyramidal dysfunction may also be present in AD[26], underlying some of the increased muscle tonus, there is absent information how this could affect postural control in AD.

Cognition and emotion

Postural control involves complex higher-level neurocognitive processes, tuned to supra-postural cognitive activity (e.g. talking while walking), so that unexpected perturbations or distractions can be resisted and/or responded appropriately, in different environments[27]. In other words, postural control is also dependent on the cognition, emotional and arousal status of the subject[20]. In that sense, postural control is a continuous fluctuation process, due its reliance on both exogenous (e.g. visual, auditory, somatosensory inputs) and higher level endogenous sources (e.g. thinking)[28]. Extensive research has shown that endogenous sources such executive function and attention have an important role in the control of balance during standing and walking [29] [30]. Individuals who have limited cognitive processing due to neurological impairments, such as IPD[31] and AD[32], when using more cognitive resources to control posture, increase inadvertently their susceptibility to falls[33]. Yet, more research is needed to differentiate the role of executive and attention networks (critical for postural control) from intruding noise or erratic endogenous cognition (networks not primarily related to postural control), in postural instability.

1.2. Spinal and suprapsinal networks

Human movement, regardless of whether movement initiation is volitional or emotional, is always accompanied by automatic processes, such as the generation of rhythmic limb movements and the regulation of postural muscle tone[20]. These processes, integrating different systems (visual, somatosensory, vestibular, auditory and even cognition), happen in spinal and supraspinal networks. Knowledge of these networks, in particularly its dopaminergic and non-dopaminergic nature, is paramount to comprehend the phenomenon underlying each

system role in postural control, especially in neurological diseases. Thus, a brief review of spinal and supraspinal networks is presented in the following paragraphs.

Supraspinal networks

In order to perform a voluntary movement, with gait and/or postural changes, motor programs, formed in the temporoparietal cortex[20], are transmitted to the brainstem by the corticoreticulospinal system, so that one's posture is always anticipatorily controlled. It is this anticipatory postural control, provided by the corticoreticulospinal system, in a closed loop with the motor cortical areas and the basal ganglia and the cerebellum, that ultimately enables the corticospinal system to generate voluntary body and limbs movement without losing balance or falling. Attention and executive networks, are also fundamental for voluntary tasks. In contrast, automatic tasks, such as adjustment of postural muscle tone and rhythmic limb movements, rely on subcortical structures, including the basal ganglia, brain stem and cerebellum[34]. While the basal ganglia contributes to planning, programming, and gait initiation, the cerebellum modulates locomotor rhythm and postural muscle tone during locomotion[20]. In the brainstem, nucleus such as the PPN, MLR and the nucleus basalis of Meynert (nbM), and their dense connections with the cortex, cerebellum, STN, and the spinal cord, also have an important role in postural and gait control[35].

Several neurotransmitters are at work in these different cortical and subcortical networks. The basal ganglia receives inputs from the cerebral cortex and controls volitional, automatic, and emotional processes through gamma-aminobutyric acid (GABA)ergic projections to the cerebral cortex, brainstem, and limbic system, respectively. The cerebellum, where Purkinje cells use GABA as their main neurotransmitter, regulates volitional, by acting on cerebral cortex, and automatic processes, by acting on the brainstem. The cerebellum exerts its function in a real-time sensory feedback from the spinocerebellar tract and feed-forward information from the cerebral cortex by the olivocerebellar tract[20]. The GABAergic output from the basal ganglia is controlled by the midbrain dopaminergic projection. Dopamine is an important neurotransmitter in the cortico-striatum-thalamo-cortical loop, but other neurotransmitters, such as ACh and noradrenaline, are equally important in postural control. ACh comes from three primary sources: cholinergic interneurons in the striatum; the nbM, which is the primary source of ACh to the cortex and basal forebrain; and the PPN, which supplies cholinergic input to the thalamus and spinal cord. ACh has different functions depending on its source and networks[20]. ACh in the thalamus, supplied primarily by the PPN, seems to be related to postural control (e.g., postural sway and sway variability), whereas cortical cholinergic function, supplied by the nbM, may be related to gait speed and hypokinesia [35].

Spinal networks

Somatosensory information travels along different anatomical pathways, from the nerve cells called "sensory receptors" (thermoreceptors, mechanoreceptors, chemoreceptors and nociceptors) to the spinal cord and brain. In the perception provided by the somatosensory

system, there are conscious and unconscious modalities. Conscious proprioception is mainly ensured by posterior column-medial lemniscal pathway (carries discriminative touch and proprioceptive information from the body) and the main sensory trigeminal pathway (carries this information from the face). However, most of the postural control as well as coordination is carried through an unconscious proprioception modality[20]. Afferent nerve fibers arising from muscle spindles and Golgi tendon organs in this limb joints, convey information to interneuronal spinal networks or to the ipsilateral spinocerebellum (anterior lobe and paramedian lobule) along the dorsal spinocerebellar tract (C8-T3 level) and cuneocerebellar tract (above C8 level). At the spinal level, the interneuronal networks, termed central pattern generators (CPGs), generate rhythmic locomotor activity [20]. These CPGs integrate descending signals from the cerebellum, brainstem and cerebral cortex, with signals coming from proprioceptive and skin afferents, to generate signal to motoneurons innervating ipsilateral limb muscles through their excitatory and inhibitory actions[20]. The rhythm and pattern of CPG are transmitted back to the supraspinal structures by the spinothalamic, - reticular, and -cerebellar tracts, so that the supraspinal structures monitor all events in the spinal cord. This real-time proprioceptive feedback concerning muscle tone, length and tension, relaying at spinal and suprapsinal networks, is critical to enable the automatic adjustment of force and length in extensor muscles, thus enabling transition from stance to swing phase [20].

1.3. Postural control in neurodegenerative diseases

In IPD disease, all the three components of postural control - maintaining, achieving, and restoring a state of balance during movements and posture - are impaired and they affect gait and postural control[5]. Postural instability, generally a manifestation of the late stages of the disease[36], is one of the most disabling clinical features increasing the risk of falls[11]. The characteristic flexed postural alignment in IPD, which results in a forward position of COM, is possibly an automatic protection against the propensity to backward falling [11]. Vascular Parkinsonism (VPD) is a Parkinsonian syndrome typically characterized by lower body parkinsonism, marked gait difficulty, less tremor, less rigidity and better hand dexterity, relatively symmetrical symptomatic distribution, association with pyramidal tract signs, more frequent dementia, and also poor response to levodopa treatment when compared to IPD [37]. Also in VPD, falls are very frequent feature [37,38]. However, there are no consensus clinical criteria for VPD, and recently some researchers have raised significant doubts about this entity[39]. In this sense, further research on gait and postural analysis in VPD [40] is needed, not only for differential diagnosis with IPD but also to better define profiles with higher postural instability and impairment and risk of falls. AD is a neurodegenerative cortical disorder that is also associated with postural and gait disturbances, which predisposes to higher risk of falls when compared to non-demented elderly people[41]. Patients with AD demonstrate a decline in

postural control due to impairment in sensory organization, or suppression of visual or auditory distractions, dual-tasking, and diversion of attention to another focus[42].

There is abundant evidence that upon deficits in one of the sensory systems (e.g. vestibular loss), humans can effectively rely and compensate with the remaining systems in order to achieve a good postural balance[43].One extreme example of this compensation has been shown in blind individuals where, probably due to cortical plasticity, passive tactile spatial acuity is enhanced when compared to sighted individuals of the same age[44]. These are the premises behind the theoretical and conceptual model of postural control, in which there is a "body schema" that results from the constant and dynamic reweighting of multisensorial integration[45,46]. However, even though this conceptual model sounds attractive, it raises many questions. The main question concerns the time frame on which the body schema adapts and reweights the different systems (e.g. normal dynamic conditions in daily life; acute disease; chronic disease). This leads to the second question, that is how can we translate postural control models to neurodegenerative diseases. Even with intact peripheral system, it is still questionable, what is the main culprit of higher postural instability in neurodegenerative diseases. How much of the postural instability is due to impairment of one of the multiple systems involved postural control, including cognition, or in contrast due to inappropriate integration, delayed processing or even higher susceptibility to intrusive auditory, visual or dual-task distractors?

1.4. Methodological strategies used on postural control analysis

Different apparatus and paradigms have successfully been used in the research of postural control, allowing on one hand to conceptualize on the human postural control model[47], and on the other to differentiate healthy subjects from patients[48-50]. Each apparatus and paradigm has its own advantages and disadvantages that have to be recognized.

Wearable devices and virtual reality

Most of the clinical research in gait and postural control has been dominated by qualitative clinical rating scales obtained by medical interpretation. Smaller and more portable accelerometer and gyroscope boards, have rendered significant advances in the field of kinetics analysis[51]. In recent years, we have observed an outstanding increase in research of gait and postural control, especially in IPD, using these wearable devices. Wearable devices are small, fully portable that are independent of the inclination in space, and have proved to be equivalent to force platforms in the measurement of the center of mass (COM) and stability analysis[52]. Wearable devices are allowing translation of clinical assessment from the hospital gait lab to the daily living conditions and different environment scenarios [53]. These new technologies, may provide a quantitative and objective analysis, overcoming some of the issues related with clinical assessment such as subjectivity. VR is a new technology that provides good replication of ecological environments with the added benefit of increasing multi-sensory immersion[54]. In

the daily life, individuals have to deal with visual, auditory, and somatosensory stimulus, very commonly under unpredictable conditions (e.g. a car crossing a street), or even under incongruent or absence of information (e.g. darkness during night). That saying, VR paradigms could be an additional tool in the differentiation of each system of postural control per si and better knowledge of the human postural control model.

Stance, compensatory postural adjustments and dual-task paradigms

One of the most successful paradigms used in postural control analysis, is the quiet stance, with feet together, staying as quite as possible with arms along the body[55]. This paradigm is the equivalent to the Romberg stance used during the neurological examination. Undoubtedly, this paradigm has the merit to isolate different systems (e.g. the influence of vision, after eyes closed, on postural control). As so, this paradigm was the common ground used in our research to investigate the role of visual, auditory, somatosensory in different neurological diseases. Yet, the advantage of this paradigm from a hospital lab perspective and conceptualization of the human postural control model[55], is counterbalanced by its lack of ecological correspondence in normal life[56]. In the daily life, the human subject is more commonly subjected to unpredictable postural challenges, where the different systems have to be dynamically reweighted in order to maintain the body within limits of postural stability[57]. In this sense, postural control adjustments paradigms may be a better approximation of real life. APA and CPA strategies are the two main mechanisms used by the CNS in order to deal with body perturbations that may either be internally generated (e.g., self-initiated movements) or externally generated (e.g., being pushed at shoulder level while walking) [57,58]. Restoring balance after an external perturbation relies on cortical, basal ganglia, and brain stem structures[59]. In fact, there is evidence that the ability to quickly adapt postural responses based on task and environmental context is altered in IPD, due to bradykinesia and rigidity and temporal uncoupling of posture (e.g. trunk lean) and gait (i.e. stepping) [60,61]. In AD, as in IPD, patients have a slower postural reaction times to external perturbation which is associated with increased risk of falling[62]. An increased contribution of cortical structures, involved in motor attention (premotor cortex) and in the body's schema representation (parietal lobe), is required when the postural tasks are more complex or difficult[63]. Patients with AD[32] and IPD[31] have been shown to be more susceptible to dual-tasking and diversion of attention to another focus (e.g. counting backwards while walking; visual distractors), showing impaired ability to re-weight and integrate multisensorial inputs, predisposing to falls. In these perspective, placing subjects in dual-task or conflicting sensorial cognitive environments, constitutes a very useful paradigm to study the cortical role in postural control and its impairment in neurological diseases.

CHAPTER 2 – OBJETIVES AND METHODS

Taking into account the above context and open questions regarding the multisensorial integration in postural control, especially in neurodegenerative diseases, we conducted our research with the following goals in mind:

1) Investigate the role of the vision system on postural control, its interaction with the somatosensory system, and define postural sway profiles related to higher risk of falls in AD, IPD and VPD.

2) Define the role of the auditory system on postural control, and the influence of cognition in suppressing auditory distractors.

3) Comprehend the impact of muscle tone on postural control and the role of levodopa on the postural control of IPD and VPD.

4) Analyze CPA and underlying spinal and supraspinal postural control networks in AD and IPD

In order to achieve these objectives, we describe below the methodology that supported our research.

2.1. The role of the visual system in postural control

AD is a neurodegenerative cortical disorder associated with postural and gait disturbances, which predispose the individual to more serious falls, when compared to non-demented elderly people[41]. AD demonstrates a decline in postural control due to cortical deficits associated with impairments of sensory organization, such as suppression of visual distraction[14], increasing their risk of falling[33]. Nevertheless, not all underlying mechanisms leading to falls have been fully understood, even less on how to identify profiles in AD presenting with higher risk of falling. Our main objective was to investigate if AD patients have higher reliance on visual input and thus, are more susceptible to visual deprivation. Also, we aimed to investigate how the visual system correlates with the somatosensory system and how postural control reweights these systems.

In order to achieve these objectives, we evaluated postural stability in 20 AD patients (11 fallers and 9 nonfallers) and 16 healthy controls with an inertial measurement unit (triaxial accelerometers and gyroscopes) attached to the center of mass (COM) in different balance conditions (Romberg on flat surface and frontward/backward- inclined surface, with or without visual suppression). This apparatus was designed to mimic increasingly difficult postural

conditions, vision suppression and susceptibility to inclination, resulting in increased compensation of the different postural control systems.

2.2. The role of the auditory system in postural control

With ageing, impaired sensory and motor systems increase the load on central processing to maintain postural balance. Patients with AD demonstrate a decline in postural control due to impairment in sensory organization, or suppression of visual or auditory distractions, dual-tasking, and diversion of attention to another focus[42]. However, it is still questionable in AD to what extent postural instability is due sensory and motor system failure and/or central integration and processing. The role of the auditory system in postural control is not properly clarified, and to our knowledge it has never been studied in AD. In our study, we aimed to comprehend the effect of background noise on postural balance, and how postural control reacts upon its suppression. Secondly, we seek to understand how visual and auditory sensorial systems integrate with each other. Lastly, we questioned if AD patients were more susceptible to any of these sensorial manipulations.

To address these objectives, we examined 24 patients with AD and 24 healthy age-matched subjects with kinematic postural analysis under four different conditions: stance with eyes open and eyes closed, with and without suppression of background noise (using ear defenders). The weight of the visual and auditory system in postural control were analyzed independently and in conjunction.

2.3. The role of levodopa and muscle tone in postural control

Postural control depends on the musculoskeletal system status of the body (muscles, bones, tendons and ligaments) since it consists of the end effector of all postural adjustments. Dopaminergic therapy, in particular levodopa, is effective on improving hypokinesia and limbs rigidity[22]. However, levodopa may not improve axial rigidity [23]. In fact, the role of levodopa on postural control remains controversial. After levodopa, some postural balance abnormalities can improve[64], but others can even worsen, probably due to levodopa-induced dyskinesia [22]. Vascular Parkinsonism (VPD) is a Parkinsonian syndrome typically characterized by lower body parkinsonism, marked gait difficulty, less tremor, less rigidity, better hand dexterity, relatively symmetrical symptomatic distribution, association with pyramidal tract signs, more frequent dementia, and poor response to levodopa treatment compared to IPD [37]. However, there are no consensus clinical criteria for VPD, and recently several researchers have raised significant doubts about this entity[39]. In VPD, the role of levodopa is not properly studied. We tried to clarify the role of the musculoskeletal system in postural control, in particular muscle

tone, and the role of levodopa. Lastly, we hypothesized if IPD and VPD present different profiles of postural control and its response to levodopa.

To clarify these questions, we purposely included only the akynetic-rigid subtype of IPD (10 patients), clinically matched as possible to VPD patients (5 patients), and performed a postural stability kinematic analysis. Different standing tasks were performed (normal stance (NS), Romberg eyes open (REO) and Romberg eyes closed) before and after levodopa challenge.

2.4. Compensatory postural adjustments

The ability to quickly adapt postural responses based on task and environmental context, and external perturbations is altered in neurodegenerative disorders, such as AD and IPD[60,65]. AD patients, even with an intact peripheral sensory system, have impaired ability to quickly re-weight central sensory dependence in response to unexpected body perturbations [62]. In IPD the ability to quickly adapt postural responses based on task and environmental context is compromised, due to bradykinesia, rigidity, temporal uncoupling of posture (e.g. trunk lean) and gait (i.e. stepping) and inappropriate scale of the size of postural response [60,61],

In our experiment, we aimed to study compensatory postural adjustments (CPA) in a goggles virtual reality (VR) visual-vestibulosomatosensory conflicting paradigm –i.e. a changing scenario, on top of a stairs, with unpredictable and random visual downward displacements - mimicking the illusion of falling. We analyzed CPA by means of kinematic and time-frequency analyzes with our werable IMU, placed on the COM (with the same methdological apparatus of our previous work). Signal was separated on different time frames (immediately before (-4s to 0 s), immediately after visual perturbation (0s-4s, immediate CPA) and delayed CPA (4s-8s). Based on other researchers findings, we aimed to verify if different networks contributing to CPAs, i.e. mechanical versus central networks, are enclosed in the raw postural sway signal and manifest on distinct time scales and frequency bands (low (<1.5 Hz) and high (>1.5 Hz). We also investigated if CPAs have a role on the risk of falling.

In order to address these objectives, we enrolled 19 healthy subjects (Controls) and 15 IPD patients, analyzed in the OFF and ON state. On a parallel work, we used the same Control group for comparison with 21 AD patients, divided according to previous history of falls (AD fallers vs AD non-fallers group).

CHAPTER 3 – RESULTS

In the following chapter, we present the results of our research, published in the form of indexed journal articles. The temporal sequence of the articles respects the timeline of our research, in particular the development of the technological apparatus. This apparatus underlies the methodology that we have used to address the proposed questions and objectives.

Chapter 3.1.

Miguel F. Gago, Vitor Fernandes, Jaime Ferreira, Hélder Silva, Luís Rocha, Estela Bicho, Nuno Sousa.

Postural stability analysis with inertial measurement units in Alzheimer's disease.

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Original Research Article

Postural Stability Analysis with Inertial Measurement Units in Alzheimer's Disease

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Key Words

Alzheimer's disease · Postural stability · Inclined surface · Inertial measurement unit · Triaxial accelerometer and gyroscope

Abstract

Background: The cause of frequent falls in patients with Alzheimer's disease (AD) is still not well understood. Nevertheless, balance control and sensory organization are known to be critical for moving safely and adapting to the environment. ***Methods:*** We evaluated postural stability in 20 AD patients (11 fallers and 9 nonfallers) and 16 healthy controls with an inertial measurement unit (triaxial accelerometers and gyroscopes) attached to the center of mass (COM) in different balance conditions (Romberg on flat surface and frontward/backward-inclined surface, with or without visual suppression) in a motor lab. ***Results:*** In AD patients, the group of fallers showed a different kinetic pattern of postural stability characterized by higher vulnerability to visual suppression, higher total/maximal displacement and a medio-lateral/anteroposterior range of sway, and a consequent need for more corrections of COM pitch and roll angles. ***Conclusion:*** Further studies are needed to consolidate the normative values of the discriminatory kinetic variables with the potential of inclusion in a multifactorial analysis of the risk of falls. Nevertheless, these results highlight signs of impairment of central postural control in AD, which may require early therapeutic intervention.

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Introduction

Alzheimer's disease (AD) is the major cause of dementia in the geriatric population in the United States and Western Europe [1]. It is a neurodegenerative cortical disorder associated with posture and gait disturbances and a high risk of falls [2]. In AD patients, falls are more frequent and have more serious traumatic consequences, including hip fracture, than in nondemented elderly people [3, 4].

The underlying mechanisms contributing to falls in AD patients are not clearly understood [5]. Physiological deficits, such as impairment of sensorimotor function, reduced vision [6], peripheral sensory loss and muscle weakness [7] and slowed reaction time [8], either individually or globally [9], detected by a Physiological Profile Assessment test [10], may explain the higher risk of falls in AD. Also, the great variability in gait patterns [11] and increased postural sway [12] may account for this higher risk of falls in AD.

Most postural kinetics studies in AD are based on postural analysis of the center of pressure on force plates. In contrast, inertial measurement units (IMU), with integrated accelerometers and gyroscopes, are small, fully portable devices that are independent of the inclination in space and have proved to be equivalent to force platforms in the measurement of the center of mass (COM) and stability analysis [11–13]. Also, IMU have the advantage of measuring postural stability in several stability and environment scenarios, including inclined surfaces.

Herein, we aim to (1) analyze postural kinetics with IMU in AD patients and healthy controls in different postural stress conditions, such as Romberg, visual suppression, and inclination and (2) try to identify discriminative kinetic parameters in AD patients that may be predictors of falls.

Methods

Subject Selection and Clinical Assessment

The study population was recruited from our hospital outpatient neurology department. Patients with probable AD, according to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [13], were consecutively recruited for the study. The control group included age-matched caregivers of patients that had no history of falls or of neurological or psychiatric disease. Patients or controls were also excluded if there was a history of orthopedic, musculoskeletal or vestibular disorder or alcohol abuse. Demographic data and medical history were collected in both groups. A brief neuropsychological examination was performed using the Portuguese version of the Montreal Cognitive Assessment test (MoCA) with scores normalized to the Portuguese population [14], no more than 1 month prior to the kinetic assessment. Levels of education were categorized by years of schooling: 0 (analphabetic), 1 (1–4 years), 2 (5–9 years), 3 (10–12 years), and 4 (>12 years). The severity of dementia was graded according to the Clinical Dementia Rating (CDR) [15]. AD patients were recorded as fallers (ADF) if they had at least one fall in the previous 6 months. Written consent was obtained from all subjects or their legal guardians, and the study protocol was approved by the local ethics committee.

Kinetic Postural Acquisition and Assessment

Biometric data [weight, height, body mass index, and anthropometric measurements, i.e. shank (ankle-knee) and thigh (knee-iliac crest)] were collected on the day of kinetic postural assessment. Five kinetic sensing modules, harboring an 8051 microprocessor embedded in

CC2530 Texas Instruments SoC (System on Chip) and an IMU MPU6000 (triaxial accelerometer and gyroscope) [16, 17] and operating with a sample rate frequency of 113 Hz on an SD card, were attached by Velcro bands to five body segments: trunk (COM; at 55% of a person's height above the ground) [18], both legs (middle of ankle-knee distance), and both thighs (middle of knee-iliac crest distance). The video capture (sample rate of 60 fps) and the data logging on the five kinetic sensors were synchronized by bidirectional radio signal transmission by an USB coordinator node (connected to a PC with custom-made Matlab software). Outputs from the accelerometers were filtered with a second order Butterworth low-pass filter with a cutoff frequency of 0.5 Hz [19], and the outputs from the gyroscopes filtered with a cutoff frequency of 5 Hz [20].

Final pitch and roll angles were obtained by a complementary filter of accelerometer and gyroscope pitch and roll (β-coefficient of 0.98) [21].

$$Pitch\ (\theta) = \beta \cdot (pitch\ (\theta)_{gyro}) + (1 - \beta) \cdot pitch\ (\theta)_{accel}$$
$$Roll\ (\phi) = \beta \cdot (roll\ (\phi)_{gyro}) + (1 - \beta) \cdot roll\ (\phi)_{accel}.$$

The kinetic sensor orientation in space was calculated by Euler angle spatial representation for pitch (θ) and roll (ϕ) [22, 23]. After definitions of angles, displacement (d) of the COM (H_{COM}; i.e. 55% of a subject's height) was calculated with the formula:

$$dy = \sin\ (pitch\ (\theta)) \cdot H_{COM};\ dx = \sin\ (roll\ (\phi)) \cdot H_{COM}.$$

One of a normal human's mechanisms of maintaining balance is to vary COM by bending knees and trunk. Therefore, the height of COM was constantly adjusted, using the information derived from the length (L) of the shank and thigh (i.e. L_{shank} and L_{thigh}, respectively) and from the angles of the IMU located on the shank and thigh (i.e. θ_{shank} and θ_{thigh}, respectively) by the formula:

$$T_1 = \cos\ \theta_{shank} \cdot L_{shank}$$
$$T_2 = \cos\ \theta_{thigh} \cdot L_{thigh}$$
$$H_{COM} = H_{COM}{}^{measured} - (L_{shank} - T_1) - (L_{thigh} - T_2).$$

From the kinetic measurements derived from the COM displacement, we focused on some that emerged from a systematic review as predictors of falls among elderly people [24]: total displacement (cm) on the transverse plane

$$\sqrt{\left(x_{i+1} - x_i\right)^2 + \left(y_{i+1} - y_i\right)^2};$$

maximal displacement (cm) with respect to the origin on the transverse plane

$$\text{maximum of } \sqrt{x_i^2 + y_i^2};$$

maximal linear velocity (cm/s) [20]; positioning (cm) on x- and y-axis (mean and range); roll angle (degrees; maximal, minimum, and mean), and pitch angle (degrees; maximal, minimum, and mean).

Test Conditions

Subjects were instructed to perform six different standing Romberg conditions: Romberg test with eyes open/closed on a flat firm surface and Romberg test on a backward/frontward-inclined surface with eyes open/closed. Subjects performed the Romberg test barefoot, with the medial aspects of the feet touching each other. During the tasks, the subjects stood quietly, with their arms hanging at their sides and their head in a normal forward-looking eye position with the eyes directed to an object 2 m away. All tasks were explained, and subjects had the opportunity to practice before the definitive trial. Each task was performed during 30 s, and

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Table 1. Demographic, clinical, and anthropometric data of controls and AD patients (ADNF and ADF)

	Controls (n = 16)	AD patients		Intergroup comparison	p
		ADNF (n = 9)	ADF (n = 11)		
Females/males, n	6/10	7/2	7/4	$\chi^2 = 4.02$	0.095
Age, years	72.31±7.08	73.56±8.72	77.64±4.80	$\chi^2_{KW}(2) = 3.77$	0.152
Level of education[1]	1 (0, 4)	1 (0, 2)	1 (0, 2)	$\chi^2_{KW}(2) = 4.383$	0.110
Height, m	1.60±0.11	1.52±0.06	1.53±0.08	$\chi^2_{KW}(2) = 5.208$	0.074
Weight, kg	71.68±9.07	68.90±9.82	65.01±7.84	$\chi^2_{KW}(2) = 4.084$	0.130
Body mass index	27.92±3.44	29.88±5.15	27.80±2.84	$\chi^2_{KW}(2) = 0.572$	0.751
COM, cm	88.27±6.04	83.99±3.33	84.15±4.29	$\chi^2_{KW}(2) = 5.208$	0.074
Duration of disease, years	–	3.33±1.94	2.82±1.47	U = 38.0; z = –0.906	0.407
CDR[1]	–	1 (0.5, 2)	2 (0.5, 2)	U = 43.5; z = –0.490	0.726
MoCA	24.75±3.59	12.22±6.63	10.09±4.42	$\chi^2_{KW}(2) = 24.023$	<0.001
				C vs. ADNF	<0.001
				C vs. ADF	<0.001
				ADF vs. ADNF	0.643

Unless otherwise indicated values represent mean ± SD. C = Controls.
[1] Values in parentheses represent minimum and maximum.

during that time the kinetic data were recorded [25, 26]. The trial was invalidated and started again if subjects moved any part of their body, spoke, opened their eyes for visual aid or did a corrective step.

We set up a fixed 15° inclined platform to standardly compare the adjustments of posture under inclination between the 3 groups. In our laboratory, on experiments of steps of 5° of inclination, healthy subjects started to have a significant change on kinetic measurements after 15° of inclination, being approximately the 20° proposed by other studies [27]. The subject were in the Romberg position, with heels below toes for the task with the backward-inclined platform, and on the same inclined platform, with toes below heels for the Romberg task with the frontward-inclined platform. They rested between test conditions to reduce the effect of muscular fatigue, especially with platform tasks [28].

Statistical Analysis

Gender comparisons were analyzed by the χ^2 Fisher exact test. Due to the absence of normality and variance equality amongst groups regarding continuous variables (anthropometrics, MoCA, years of disease, and kinetics parameters) and ordinal variables (education and CDR), the comparison between the groups was carried out by a nonparametric test, the Kruskal-Wallis test (comparison between 3 groups), with a pairwise post hoc analysis with Dunn's test and the magnitude of change in intraindividual tasks by the Wilcoxon matched pair test. Correlation analyses of age, anthropometrics, CDR and years of disease, with kinetic data, were performed with the Spearman test. All statistical analyses were conducted with statistical analysis software (SPSS 20.0) using a 95% level of significance.

Results

Demographic, Clinical, and Anthropometric Data

This study included 20 AD patients [9 classified as nonfallers (ADNF) and 11 as ADF] and 16 controls. There were no statistically significant differences between the groups, regarding age or anthropometric parameters (table 1). In spite of a higher frequency of females in the

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Table 2. Inertial measurement unikinetic analysis in different conditions

Conditions	Kinetic variables													
	path, cm		velocity, cm/s	x-axis position		y-axis position		roll angle, degrees			pitch angle, degrees		
	total displacement	maximal displacement	max	mean	range	mean	range	max	min	mean	max	min	mean
Romberg on flat surface													
Eyes open													
Controls	18.67±3.13	2.76±0.98	0.95±0.51	0.84±0.87	2.14±0.69	–0.20±1.2	2.96±1.15	0.73±0.48	–0.65±0.50	0.09±0.46	0.83±0.87	–1.09±0.77	–0.11±0.72
ADNF	20.77±5.96	2.5±0.99	0.81±0.37	1.00±0.79	2.20±0.93	0.02±1.04	2.90±1.22	1.07±0.62	–0.46±0.52	0.30±0.46	1.00±0.79	–0.97±0.74	0.02±0.73
ADF	23.85±5.85	2.82±1.80	1.29±0.70	1.11±0.76	3.10±1.70	0.28±0.90	2.65±0.96	1.29±1.35	–0.84±0.57	0.22±0.82	1.11±0.76	–0.69±0.63	0.20±0.60
Eyes closed													
Controls	21.73±4.95*	2.44±0.82	0.72±0.17	0.91±0.54	2.31±0.96	0.02±0.80	2.79±0.80	0.70±0.60	–0.80±0.60	– 0.04±0.59	0.91±0.54	–0.89±0.59	0.02±0.53
ADNF	22.79±7.04	2.37±1.06	0.95±0.55	0.95±0.67	2.53±1.34	0.09±1.02	2.55±1.02	0.62±0.41	–1.11±0.74	– 0.20±0.44	0.95±0.67	–0.80±0.78	0.05±0.69
ADF	32.21±11.56*	4.26±2.18*	2.17±1.30	2.01±1.43	4.26±2.61	0.97±1.44	4.04±1.84*	1.67±1.20	–1.25±1.16	0.13±0.70	2.01±1.43	–0.73±0.72	0.65±0.96
Romberg on backward-inclined surface													
Eyes open													
Controls	21.58±6.35	2.74±1.34	1.17±0.64	0.66±0.83	2.34±1.02	–0.38±1.44	2.65±1.42	0.81±0.50	–0.73±0.76	0.003±0.56	0.66±0.83	–1.04±0.95	–0.25±0.90
ADNF	25.05±11.12	2.77±1.31	1.63±1.48	1.17±0.84	2.99±2.09	0.36±0.87	2.67±1.12	0.99±1.09	–1.08±0.82	– 0.05±0.63	1.17±0.84	–0.68±0.37	0.26±0.61
ADF	26.22±8.07	2.86±1.46	1.83±1.43	1.03±0.88	3.13±0.88	0.32±0.73	2.31±1.14	1.47±0.98	–0.67±0.56	0.36±0.72	1.03±0.88	–0.53±0.43	0.22±0.50
Eyes closed													
Controls	24.88±8.46	2.73±1.27	1.46±0.77	1.17±0.85	2.45±0.96	0.30±1.23	3.01±1.14	0.75±0.64	–0.84±0.57	–0.026±0.55	1.17±0.85*	–0.79±0.82	0.19±0.82
ADNF	23.81±14.80	2.51±1.30	1.74±1.23	1.11±0.59	2.64±1.58	–0.08±0.59	3.45±1.99	1.14±0.76	–0.66±0.44	0.22±0.37	1.11±0.59	–1.23±0.91	–0.05±0.41
ADF	33.90±12.85*	3.47±1.95	2.29±1.19	1.09±0.77	3.70±1.79	–0.00±0.94	3.19±1.44*	1.56±1.74	–0.94±0.74	0.23±1.04	1.09±0.77	–1.06±0.58	–0.01±0.64
Romberg on frontward-inclined surface													
Eyes open													
Controls	20.65±6.15	3.35±2.25	1.55±1.06	1.42±1.58	2.17±1.11	0.39±1.39	3.59±2.60	0.62±0.55	–0.80±0.59	– 0.10±0.46	1.42±1.58	–0.92±1.22	0.27±0.91
ADNF	23.85±7.93	2.78±1.95	1.40±1.34	1.26±1.60	2.55±0.92	0.46±1.83	3.21±2.00	0.76±0.47	–0.99±0.59	– 0.06±0.41	1.27±1.60	–0.95±0.59	0.34±1.28
ADF	26.03±8.20	3.34±1.47	1.16±0.59	1.61±1.04	2.82±1.31	0.77±1.44	3.33±1.09	0.93±1.11	–1.00±0.65	– 0.09±0.64	1.60±1.04	–0.67±0.62	0.53±0.98
Eyes closed													
Controls	24.03±7.86	2.50±1.38	1.40±0.93	0.82±0.69*	2.24±0.89	–0.08±1.14	2.28±1.58	0.97±0.59	–0.48±0.42	0.24±0.37*	0.82±0.69	–0.98±0.94	–0.05±0.76
ADNF	28.89±10.64	2.95±0.97	1.66±1.08	1.05±0.95	2.94±1.12	–0.48±0.91	3.61±1.46	1.06±0.65	–0.94±0.60	– 0.04±0.53	1.05±0.94	–1.42±0.57	–0.31±0.61
ADF	32.80±13.18	3.23±1.16	1.80±1.59	0.78±0.70	3.32±1.53	–0.66±1.19*	3.49±1.29	1.02±0.59	–1.26±0.98	– 0.18±0.71	0.78±0.70	–1.60±0.83*	–0.45±0.78*

Data are presented as mean ± standard deviation of kinetic variables in different conditions of the Romberg test for controls, ADNF and ADF. Shaded boxes show values where there was statistical significance on Kruskal-Wallis test and post hoc analysis between the 3 groups. * Statistical significance with Wilcoxon matched pair test between eyes open and eyes closed in each condition.

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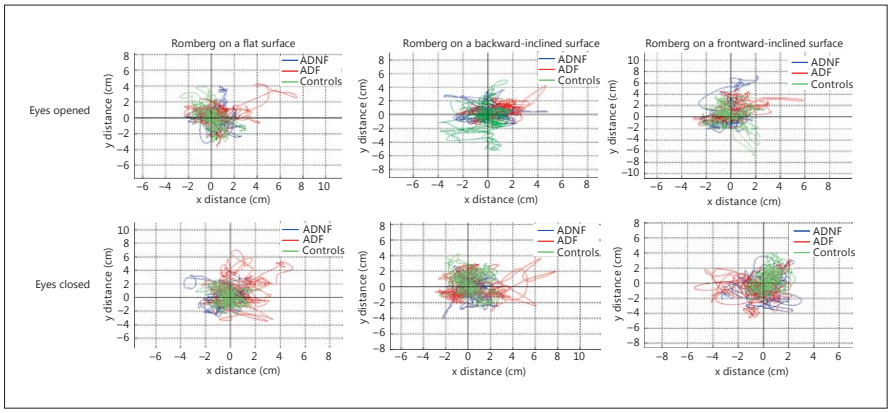

Fig. 1. Displacement plot on the x-axis (mediolateral) and the y-axis (anteroposterior) of the IMU, attached to the COM (at 55% of height), for all subjects (controls, ADF, and ADNF).

AD patients, no statistical difference was detected regarding gender between the controls and ADF and ADNF patients. Moreover, the gender has not been associated with postural sway deficits [27]. The majority of AD patients and controls had an education level of less than 4 years. As expected, AD patients had lower scores on MoCA compared to controls, but there were no differences between ADNF and ADF in the total MoCA score or its subitems. ADF patients did not differ from ADNF patients regarding years of progression or severity of AD. No correlations were found between age, CDR, or years of disease with any of the kinetic variables.

Kinetic Postural Analysis

Romberg Position with Eyes Open/Eyes Closed on Flat Surface

In the Romberg position with eyes open, the kinetic posture measurements were not statistically different between the 3 groups. With eyes closed, the groups differed in the following kinetic posture measurements: total displacement [$\chi^2_{KW}(2) = 6.608$; $p = 0.037$; controls vs. ADF $p = 0.01$; controls vs. ADNF $p = 0.447$; ADF vs. ADNF $p = 0.127$], maximal displacement [$\chi^2_{KW}(2) = 9.241$; $p = 0.01$; controls vs. ADF $p = 0.013$; controls vs. ADNF $p = 0.948$; ADF vs. ADNF $p = 0.005$], and range on x-axis [$\chi^2_{KW}(2) = 9.036$; $p = 0.01$; controls vs. ADF $p = 0.003$; controls vs. ADNF $p = 0.645$; ADF vs. ADNF $p = 0.034$] (table 2). The Wilcoxon matched pair test was used to compare between conditions with eyes open versus eyes closed, revealing that on visual suppression, controls had a statistically significant increase in total displacement ($Z = -2.689$; $p = 0.005$) and the ADF group had a statistically significant increase in total displacement ($Z = -2.490$; $p = 0.01$), maximal distance ($Z = -1.956$; $p = 0.054$), and range on y-axis ($Z = -2.134$; $p = 0.032$) (fig. 1).

Romberg Position with Eyes Open/Eyes Closed on Inclined Platform

On the backward platform, no differences were found between the groups. On the frontward platform, with eyes closed, the AD patients, in particular the ADF patients, had a lower minimal roll angle [$\chi^2_{KW}(2) = 10.442$; $p = 0.005$; controls vs. ADF $p = 0.002$; controls vs. ADNF $p = 0.468$; ADF vs. ADNF $p = 0.044$] (table 2).

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The Wilcoxon matched pair test was used to compare between conditions with eyes open and eyes closed. On the backward-inclined surface, under visual suppression, the controls had an increase in maximal pitch angle ($Z = -2.223$; $p = 0.025$) towards anterior (positive values) inclination, and the ADF patients had an increase in total displacement ($Z = -2.599$; $p = 0.006$) and the range on the y-axis ($Z = -2.395$; $p = 0.014$).

On the frontward-inclined surface, under visual suppression, controls shifted to a lower mean x-axis position ($Z = -2.120$; $p = 0.034$) and had an increase in the mean roll angle ($Z = -2.223$; $p = 0.025$). The ADF group had a significant change in the minimal pitch angle ($Z = -2.667$; $p = 0.005$) towards posterior inclination, almost reaching significance on a more posterior (negative) mean y-axis position ($Z = -1.956$; $p = 0.054$) and on a mean pitch angle ($Z = -1.956$; $p = 0.054$) (fig. 1).

Discussion

The cause of frequent falls in patients with AD is still not well understood. Balance control and sensory organization are known to be critical for moving safely and adapting to the environment. Herein, we have explored the underlying mechanisms for this tendency to fall and we have shown that ADF patients display a different kinetic profile.

Balance is a complex process of coordination of multiple body systems, including the vestibular, auditory, visual, motor and higher level premotor systems, that generate appropriate synergic postural muscle movements of the head, eye, trunk, and limbs to maintain posture [29]; this is achieved by sustaining, achieving, or restoring the body COM relative to the base of support or, more generally, within the limits of stability with a minimal sway [30]. An individual's limits of stability, commonly referred to as functional stability limits, refer to the maximum distance in which one can voluntarily displace one's center of gravity and lean one's body in a given direction without losing one's balance [31].

Visual suppression makes the human body more dependent on vestibular and proprioceptive systems, consequently increasing sway [9], which was confirmed in our study both in healthy and AD subjects. However, the visual suppression effect was stronger in ADF patients. After closing their eyes, the ADF group swayed more (total displacement) and beyond safety limits (maximal displacement). Contrary to controls that presented on visual suppression a normal correction acquiring a more central position (lower mean x- and y-axis positions and range of sway), the ADF group had an increase in the range of mediolateral/anteroposterior sway. Our results agree with previous literature which has shown that the mediolateral sway is associated with a higher risk of falls in elderly people [24], and the anteroposterior sway is a discriminative parameter of AD versus controls [9] and also of fallers versus nonfallers in cognitively able older people [32]. This increased sway also demanded more pitch and roll variations, and ankle and trunk strategies of correction of stability [33] in the ADF group.

We also aimed to evaluate the susceptibility to inclination, as AD patients can walk long distances and thus are subjected to constant environmental postural stress, such as surface inclination, which may account for their falls [34]. Postural control on a tilting support surface is mainly achieved with the help of visual, vestibular, and proprioceptive afferents [27]. On a 20° static inclined surface, the inclination was described to significantly increase postural imbalance in healthy subjects, especially when visual support was interrupted [27]. Contrary to what we had primarily expected, on the inclined surface, there was an attenuation of the differences between groups that were more evident on the flat surface. A learning trial repetition bias [35], an instruction anticipation factor, and a higher demand of attention and focus could have accounted for a better postural sway performance on the inclined surfaces in comparison to the less stressful flat surface condition. However, the controlled lab conditions

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are exactly the opposite of the daily living conditions where patients are more relaxed, unfocused, and without the anticipation effect of fear of falling [36] or preparation for episodes of disequilibrium. This clearly highlights the importance of cognition, especially attention, on postural balance [12], and the need for complementing lab analysis with kinetic studies on everyday motion behavior [37].

In a recent study, older adults with presumptive preclinical AD, with higher levels of brain fibrillar amyloid plaques measured by Pittsburgh compound B retention on brain PET imaging, had a short latency time to their first fall [38]. This raises the hypothesis that neuropathological changes that negatively affect postural control and increase the risk of falls may happen subclinically in AD patients [32, 39, 40]. In fact, in our study, ADF and ADNF patients, although having different kinetic performances, were clinically very similar, not differing in age, anthropometric data, neuropsychological assessment, or severity of the disease. Therefore, kinetic postural analysis, in our study measured with IMU, may be a useful tool to preclinically identify AD patients with a higher risk of falls.

Although we need more studies to consolidate normative values of discriminatory kinetic variables acquired by IMU, with the potential of inclusion in a multifactorial analysis of the risk of falls, our results highlight signs of impairment of central postural control in AD, which may require early therapeutic intervention.

Disclosure Statement

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Chapter 3.2.

Miguel F. Gago, Vıtor Fernandes, Jaime Ferreira, Darya Yelshyna, Hélder David Silva, Maria Lurdes Rodrigues, Luís Rocha, Estela Bicho and Nuno Sousa.

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Role of the Visual and Auditory Systems in Postural Stability in Alzheimer's Disease

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Abstract.
Background: Postural stability requires the integration of multisensory input information and translation into appropriate motor responses. Surprisingly, few previous studies have addressed the role of auditory input on postural stability in healthy subjects, and none has investigated this in Alzheimer's disease (AD).
Objective: To assess the influence of the visual and auditory systems on postural stability in patients with AD and healthy subjects.
Methods: Twenty-four patients with AD and healthy age-matched subjects were examined by kinematic postural analysis (inertia measurement units placed at the center of mass of the body) under four different conditions: stance with eyes open and eyes closed, with and without suppression of background noise (using ear defenders). The effects of visual and auditory influences were analyzed independently and in conjunction.
Results: In both groups, visual suppression had a negative impact on postural stability, while suppression of background noise, non-specifically and without spatial cues, significantly benefited postural stability. We also observed that in both groups, the positive effect of background noise suppression was insufficient to compensate for the negative effect of visual suppression, to which the patients were significantly more vulnerable.
Conclusions: Audition, albeit less significant than vision, also plays a role in the multi-sensorial dynamic control of postural stability by the central nervous system. In everyday life, audition is likely to be a relevant factor in postural stability. This is especially relevant in AD in which, even when the peripheral sensory system is intact, the central processing is impaired and sensory dependence is re-weighted.

Keywords: Alzheimer's disease, auditory system, postural stability, visual system

INTRODUCTION

Postural balance is a complex central nervous system (CNS) process involving feedback integration of multiple sensory inputs, including those from the vestibular, visual, auditory, and motor systems, based on an internal body schema [1–4]. Efficient postural balance translates into appropriate synergistic movements of the head, eyes, trunk, and limbs [5], to attain or restore the center of mass (COM) of the body relative to the base of support, within the limits of stability and with minimal sway [6]. The importance of multiple sensory feedback integration is clearly evident from the improvement in balance that occurs when

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sensory information is available. Although it has long been known that auditory spatial cues provide humans with the ability to localize sound sources moderately accurately, it remains unclear how the auditory system is involved in postural balance. Postural stability benefits from auditory feedback information on the subject's body sway, particularly in patients with bilateral vestibular deficits [7]. In contrast, other studies have shown that a static auditory stimulus can have a destabilizing influence on postural control, independent of the type of spatial location source of the auditory stimulus [8], and that a moving auditory stimulus increases lateral body sway [9].

These previous studies on the influence of the auditory system on postural control were conducted on healthy subjects, and none has been performed in patients with neurodegenerative diseases, such as Alzheimer's disease (AD). AD is a neurodegenerative cortical disorder associated with postural and gait disturbances, which predispose the individual to more serious falls, when compared to non-demented elderly people [10]. However, the contexts in which such loss of postural balance and falls occurs are not fully clear. Postural control also involves complex higher-level neurocognitive processes, as it has to be tuned to supra-postural cognitive activity, so that unexpected perturbations or distractions can be resisted and responded to appropriately in different environments [7].

The main objective of our study was to assess how visual and auditory information influence postural stability in patients with AD and healthy subjects by means of kinematic postural analysis.

MATERIALS AND METHODS

Subjects and clinical assessment

The study protocol was submitted by the ICVS and Algorithm Center and was approved by the local ethics committee, and was carried out in accordance with the Declaration of Helsinki.

Patients with probable AD, according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [11], were recruited from our hospital outpatient clinic. Controls were consecutively recruited for the study. Exclusion criteria were orthopedic or musculoskeletal disorders, proprioceptive loss, or peripheral neuropathy, vestibular disorders, visual or auditory deficits, or alcohol abuse. A brief neuropsychological examination was performed using the Portuguese version of the Montreal Cognitive Assessment test (MoCA) with scores normalized to the Portuguese population [12], at no more than 1 month prior to the kinetic assessment. Informed consent was obtained from all participants.

Apparatus and postural tasks

One sensing module, harboring an 8051 microprocessor embedded in a CC2530 *Texas Instrument* SoC (System on Chip), and a wearable inertial measurement unit MPU6000 (tri-axial accelerometer and gyroscope) [13], operating at a sample rate frequency of 113 Hz on an SD card, was attached to the center of mass (COM) (55% of a patient's height above the ground [14]). Video capture (sample rate of 60 fps) and data logging were synchronized by bidirectional radio signal transmission through an USB-based coordinator node connected to a PC with custom-made Matlab© software. We focused on kinematic measurements derived from the wearable sensor unit placed at the COM: total and radius displacement of sway (cm) with respect to origin; range of medial−lateral (ML) and anterior−posterior (AP) sway (cm), on the X- and Y-axis transverse planes, respectively. Our procedure was not a precise estimation of the COM, but rather provided an approximation of the characteristics of the displacement. Further information on our methodology and mathematical formulas for kinematic acquisition has been elsewhere published [15].

Subjects were instructed to perform four different tasks in these sequence: standing with eyes open (EO), standing with eyes closed (EC), standing test with eyes open with auditory suppression (EOAS), and standing test with eyes closed and auditory suppression (ECAS). Subjects performed the tests while standing upright and barefoot on a firm floor, with the medial aspects of the feet touching each other, for 30 s. During the tasks, subjects stood quietly, with their arms hanging at their sides and their head in a normal forward-looking eye position, directed at an object placed 2 m away, in a quiet clinical hospital room laboratory, with constant background noise mostly in the range of 125−2000 Hz (36-dB peak, as determined by frequency band spectrum analysis performed with SignalScope Pro® trial version software). In order to eliminate auditory background noise and potential auditory spatial cues, the subjects were instructed to wear commercially available industrial ear defenders (3M Peltor Optime III®), which resulted in a mean 20.8-dB noise reduction at 63 Hz and 42.6-dB reduction at 8 KHz.

A bedside neurological test (finger rub near to each ear) was used for auditory system examination, with regard to its integrity and symmetry of auditory acuity. Prior to the tests with auditory suppression, in order to exclude the potential confounding influence of wearing ear defenders, the ear defenders were placed immediately above the earlobes, serving as a pre-test comparison condition under the EO condition. However, we found that wearing ear defenders had no influence on postural sway.

The Romberg index is widely used to evaluate the contribution of vision to postural stabilization; this ratio of the parameter values was obtained under the EC and EO conditions, and is commonly greater than 1 [16]. We computed three different index scores representing the impact of the different conditions on postural stability and the relevant ratio: (a) visual suppression (Index 1; the transition from the EO to EC condition; EC/EO ratio); (b) auditory suppression with eyes open (Index 2; transition from eyes open to eyes open with auditory suppression; EOAS/EO ratio); and (c) auditory suppression with eyes closed (Index 3; transition of eyes closed to eyes closed with auditory suppression). The index score of each kinematic parameter was computed by the relevant ratio standardized to unit value 1 and transformed to a percentage (e.g., Index 1 score on total displacement = Total displacement EC/Total displacement EO – 1 × 100).

Statistical analysis

Statistical comparisons between groups in terms of gender and education were performed using Fisher's exact test. Given the small number of subjects, the absence of normality and variance equality among groups regarding continuous variables (anthropometric, kinematic parameters, Index 1, Index 2, Index 3), groups were compared using the nonparametric Mann−Whitney test. A pairwise Wilcoxon test was used for intragroup analyses of Index 1 versus Index 2, Index 1 versus Index 3, and Index 2 versus Index 3. All statistical analyses were conducted using SPSS20.0 statistical analysis software, using $p < 0.05$ as an indication of statistical significance.

RESULTS

Subjects

Twenty-four patients with AD (16 women, 8 men) and 24 controls (13 females/11 males) were included in this study. Groups were equally matched in terms of age: control 72 ± 6.4 y; AD 75 ± 6.9 y, ($p = 0.147$). Moreover, both groups had non-significant anthropometric differences in weight (control: 72.5 ± 12.4 kg versus AD: 67.2 ± 9.3 kg; $p = 0.112$), height (controls: 1.59 ± 0.09 mm versus AD: 1.55 ± 0.08 m; $p = 0.112$), and body mass index (control: 28 ± 4 kg/m^2 versus AD: 27 ± 4 kg/m^2; $p = 0.635$). As expected, the patients had lower scores on the MoCA test (control: 25 ± 4 versus AD: 11 ± 5; $p < 0.001$).

Basal differences on kinematic parameters

Patients with AD and controls differed in several kinematic parameters, with the patients presenting with greater postural sway, irrespective of the transition between the different postural stance conditions (Table 1; Fig. 1). Differences between the groups were more evident in the EC and EOAS postural stance conditions.

Visual suppression effect

In both groups, the absence of visual feedback (Index 1) had a negative impact on postural stability, increasing several sway parameters (Tables 1 and 2). Albeit there were no significant differences between the groups in the impact of visual suppression, the patients had higher Index 1 values, particularly in the range of ML sway.

Auditory suppression effect

Absence of auditory feedback (Index 2) had a positive impact on postural sway in both groups, decreasing several sway parameters (Table 2). There were no significant differences between the two groups in terms of the effect of auditory suppression. The positive effect of auditory suppression on postural stability was more noticeable on AP sway than on ML sway.

Combined visual and auditory effects

When assessing the two effects (visual and auditory suppression, ASEC condition) simultaneously, both groups returned to the values at baseline (i.e., the EO condition; Table 1). In both groups, there were no differences in terms of the positive impact of auditory suppression, neither with EO nor with EC (Index 2 versus Index 3; Table 3, Fig. 2). In patients with AD, the negative effect of visual suppression was significantly greater than the positive effect of auditory suppression (Index 1 versus Index 3; Table 3, Fig. 2); this was

Table 1
Kinematic postural sway parameters for Controls and Alzheimer's disease (AD) patients under the four different conditions (stance with eyes open [EO] and with eyes closed [EC], stance with EO and auditory suppression [EOAS], stance with eyes closed and auditory suppression [ECAS])

Kinematic Parameters	Conditions									
	EO			EC			EOAS			ECAS		
	Control	AD	*p*	Control	AD	*p*	Control	AD	*p*	Control	AD	*p*
Total displacement (cm)	18.71 ± 4.12	21.32 ± 4.79	**0.037**	20.80 ± 5.00	25.27 ± 6.23	**0.01**	15.95 ± 3.87	19.00 ± 4.51	**0.021**	19.32 ± 5.03	22.27 ± 5.83	**0.051**
Radius of displacement (cm)	0.74 ± 0.25	0.79 ± 0.24	0.439	0.78 ± 0.33	0.88 ± 0.33	0.200	0.55 ± 0.16	0.69 ± 0.19	**0.008**	0.70 ± 0.21	0.79 ± 0.28	0.381
Range of medial−lateral displacement (X-axis) (cm)	2.12 ± 0.62	2.42 ± 0.73	0.075	2.40 ± 1.10	3.01 ± 1.18	**0.033**	1.93 ± 0.81	2.31 ± 0.58	**0.046**	2.29 ± 0.78	2.51 ± 0.79	0.506
Range of anterior-posterior displacement (Y-axis) (cm)	2.60 ± 1.13	2.7 ± 1.03	0.744	2.62 ± 1.07	3.18 ± 1.19	0.099	1.75 ± 0.72	2.24 ± 0.58	**0.026**	2.41 ± 0.88	2.96 ± 2.40	0.240

Mann-Whitney *p*-values for comparison between Controls and AD groups. Statistically significant *p*-values ($p < 0.05$) are shown in bold.

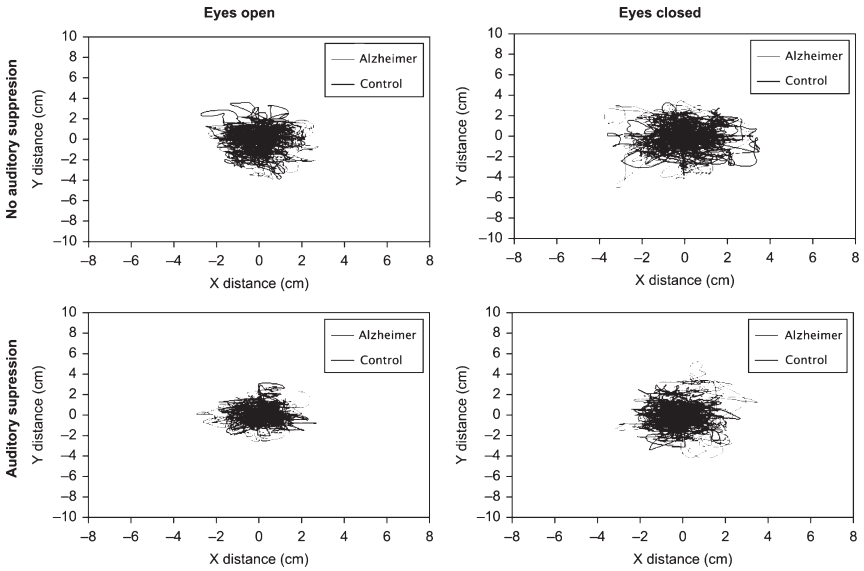

Fig. 1. Displacement on X-axis (medial−lateral) (cm) and Y-axis (anterior−posterior) (cm) of the inertial measurement unit, plotted on the different postural stance conditions (eyes open, eyes closed, no auditory suppression [background noise in a silent room] and auditory suppression of the background noise [ear defenders]) on all participants: Controls and Alzheimer's disease patients.

Table 2
Index scores for Control and Alzheimer's disease (AD) patients groups

Kinematic parameters	Index 1 (Visual suppression) EC/EO (%)			Index 2 (Auditory suppression with EO) EOAS/EO (%)			Index 3 (Auditory suppression with EC) ECAS/EC (%)		
	Control	AD	*p*	Control	AD	*p*	Control	AD	*p*
Total displacement (cm)	+12 ± 21	+20 ± 22	0.215	–14 ± 16	–10 ± 16	0.428	–6 ± 19	–11 ± 15	0.466
Radius of displacement (cm)	+8 ± 40	+15 ± 39	0.760	–18 ± 37	–7 ± 32	0.185	1 ± 44	–6 ± 30	0.666
Range of medial−lateral displacement (X-axis) (cm)	+15 ± 42	+30 ± 48	0.404	–9 ± 24	+5 ± 46	0.620	+5 ± 39	–11 ± 27	0.171
Range of anterior−posterior displacement (Y-axis) (cm)	+16 ± 58	+23 ± 45	0.441	–22 ± 40	–12 ± 33	0.285	+2 ± 45	–3 ± 33	0.958

Index scores represent the transition between the different postural stance conditions: visual suppression (Index 1); audition suppression with eyes open (Index 2), and with eyes closed (Index 3). See Methods section for further explanation on the form of calculation of these index scores on respective ratios: eyes open (EO)/eyes closed (EC); EO and auditory suppression (EOAS)/EO; and EC and auditory suppression (ECAS)/EC. Mann−Whitney *p*-values for comparison between Controls and AD groups.

evident in the total, radius, and range of ML displacement parameters. In contrast, in controls, this was only evident in terms of total displacement.

DISCUSSION

Postural control is a task-specific central process that flows from the interaction between central multisensory feedback loop integration (visual, vestibular, somatosensory, and auditory), perception-action, and behavioral constraints, in a specific environment [1–4, 17]. Little is known about how all these systems affect human postural stability, and even less so in the case of individuals with neurodegenerative disorders, such as AD. Therefore, we simultaneously manipulated visual input (visual suppression by closing the eyes) and auditory input (noise reduction by using ear defenders), on the postural stability of subjects, with a normal somatosensory system, standing on a flat and stable floor. In addition to comparing the effects of these

Table 3
Intragroup comparison (pairwise Wilcoxon test *p*-values) of index scores between Controls and Alzheimer's disease (AD) patients

Kinematic parameters	Intragroup comparison (*p*-values)					
	Index 1 versus Index 2		Index 1 versus Index 3		Index 2 versus Index 3	
	Control	AD	Control	AD	Control	AD
Total displacement (cm)	**<0.001**	**<0.001**	**0.001**	**<0.001**	0.189	0.830
Radius of displacement (cm)	**0.021**	**0.008**	0.433	**0.034**	0.087	0.976
Range of medial−lateral displacement (X-axis) (cm)	**0.042**	**0.019**	0.383	**0.001**	0.383	0.291
Range of anterior−posterior displacement (Y-axis) (cm)	**0.036**	**0.004**	0.586	0.056	0.065	0.443

Statistically significant *p*-value ($p < 0.05$) are shown in bold.

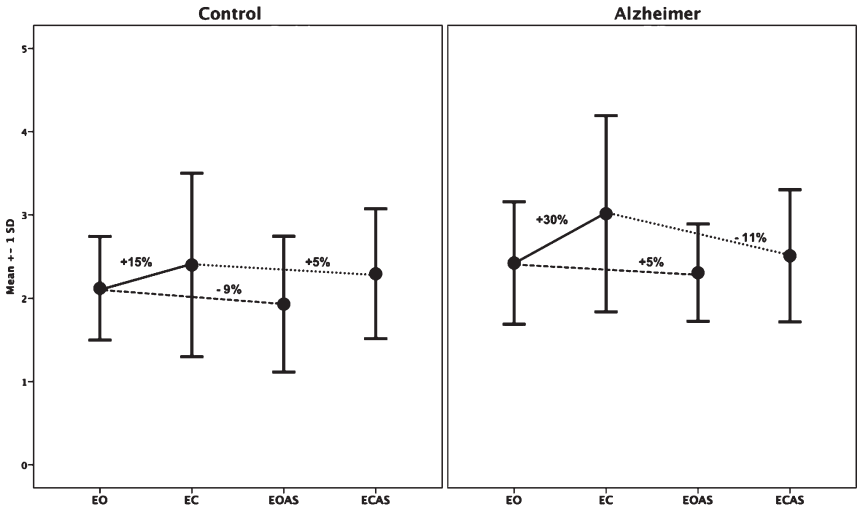

Fig. 2. Graphical comparison, errors bars (mean ± 1 SD), between controls and Alzheimer's disease patients of the medial−lateral displacement on the different postural stance conditions: eyes-open (EO); eyes-closed (EC); EO with auditory suppression (EOAS); and EC with auditory suppression (ECAS). Index scores (%mean) (see Table 2) are superimposed on the interconnecting lines that represent: Index 1 (visual suppression, represented by a straight line); Index 2 (auditory suppression with EO, represented by a dashed line); and Index 3 (auditory suppression with EC, represented by a dotted line).

sensory inputs on basal postural sway, we also analyzed the impact of the change between these conditions in patients with AD and healthy subjects.

The patients presented significant differences in postural sway, corroborating previous reports showing that patients with AD have greater postural sway both with and without visual suppression than do healthy subjects [18, 19]. It has been reported that there is a trend for increased reliance on visual control between individuals who are healthy, patients with amnesia, those with mild cognitive impairment, and those with AD [18]. Our data showed that absence of visual feedback input significantly increased the magnitude of postural sway in both control and AD groups, irrespective of the positive effect of auditory suppression. Interestingly, the higher impact on ML sway probably reflects a compensatory strategy for hip postural stability [5].

In our study, the suppression of auditory input led to improved postural stability and decreased postural sway, in both groups. The meaningless background noise, even in a relatively silent hospital laboratory, may have created more distraction than a total lack of auditory information. This is in accordance with a previous report demonstrating the destabilizing effect of background conversation on postural stability [8]. The background noise, even when patients were instructed to look at a fixed location with eyes open, may have been interpreted as vague and without any value in terms of spatial location. A correlation between

hearing and balance has been reported essentially for fixed sound sources that provide spatial localization cues [20], and particularly binaural cues [21]. It is also known that a moving auditory stimulus increases lateral sway and places more demand on the maintenance of postural stability, particularly in the elderly [9]. In one study in which young healthy subjects were assessed in different environments (normal room versus soundproof room) and conditions (eyes open, eyes closed, with and without ear defenders, and standing on foam), an increase in postural sway was noted when participants wore ear defenders or were in a soundproof room [22]. However, this was only present when the ear defenders were used in addition to standing on a foam rubber surface; thus, manipulation of proprioception may have contributed to the findings. In another study, where background noise was buffered by means of binaural headphones through which instrumental music was presented, auditory stimuli did not affect postural stability, irrespective of the visual environment (eyes open or closed) [1]. In that study, the auditory stimulus involved a sound level of 75–80 dB; instrumental music without lyrics were deliberately chosen in order to prevent the subjects from listening to the words or singing along, and thus being distracted by something other than a pure auditory stimulus. This "background noise" condition could also be considered as non-specific, similar to that used in our study, as it did not provide any fixed or moving auditory spatial cue. The authors concluded that music, which eliminates spatial acoustic information from the environment, was not associated with an increased risk of falling. Those authors suggested that future studies should test subjects when wearing headphones, but without music, which was done in our study. Even though the auditory system is of less importance than other systems (vestibular, somatosensory, and visual), acoustic information plays an important role in the maintenance of postural stability, particularly in the absence of visual cues, by providing important spatial information [1, 8, 20]. Auditory orientation is ensured by binaural cues, which involve central assessment of differences in time and intensity between the auditory inputs from the two ears, and by non-binaural cues, which influence postural alignment and the ability to locate sounds [21]. ML spatial orientation auditory cues have previously been found to reduce body sway [21]. In another study using a different protocol, mid−sagittal plane auditory cues (which rely on non-binaural cues rather than binaural medial−lateral cues), were found to have a higher destabilizing influence on postural sway [8]. Larger errors in sound localization occur when sounds arise from anteriorly or posteriorly located sources, than when sound stimuli arise laterally (from the right and left side) [8]. Interestingly, in our work, the positive auditory suppression effect on postural stability was also more evident on AP sway than on ML sway. These orientation errors are commonly offset by another compensatory system, such as visual feedback [8].

The aforementioned studies along with our own prove that auditory information is integrated with that from other sensory systems, in different scenarios and environments, in order to achieve better postural stability. In that sense, in our study, auditory suppression allowed a beneficial reallocation of cognitive resources toward focusing on better postural stability; in contrast, visual suppression had a greater negative effect, particularly in patients with AD. Although there are conflicting reports on how cognitive resources correlate with the postural control on healthy subjects [23], patients with AD demonstrate a decline in postural control due to cortical deficits associated with impairments in sensory organization, such as suppressing visual or auditory distraction, dual tasking, and diversion of attention to another focus [24–26]. Response inhibition, an executive cognitive function, allows one to ignore irrelevant sensory inputs, overcome primary reflexes, filter out distractions, respond discriminatively to important features in the environment, and focus on postural stability [27]. The impaired ability of the CNS to quickly re-weight sensory dependence in AD (even when the peripheral sensory system is intact), in response to dynamic perturbations in the sensorial environment during daily life, increases the risk of falling [24, 28]. Central processing within the primary auditory cortex and higher order association areas is required for identification and comprehension of the auditory signal. Furthermore, central auditory function is strongly associated with measures of executive function, which in turn has been implicated as an early marker for dementia [29]. It is likely that central auditory and executive functioning share cognitive resources, given that both tasks require participants to selectively attend to one stream of information while inhibiting non-relevant information [30].

This study has several limitations. The prevalence of age-related hearing loss in older adults, referred to as presbycusis, doubles with each decade of age [31]; however, in our work, control and AD groups were age-matched and, consequently auditory sensory acuity was not a confounding factor. Sounds that are audible to the human ear fall in the frequency range of about 20–20,000 Hz, with the highest sensitivity between 500 and 4,000 Hz. The background noise used

was mostly in the range 125 to 2000 Hz (36-dB peak), and the buffering provided by ear defenders may have been sufficient to cut out this noise. In our study, these potential non-measured fine auditory differences, albeit not influencing the intra-group auditory suppression effects, could have influenced differences between groups. The integrity and symmetry of the auditory system was qualitatively determined by neurological examination; however, the use of audiometry would have provided more objective data.

CONCLUSION

Our results have proven that auditory information plays a role in the multi-sensorial dynamic control of postural stability by the CNS. Blocking background noise, which was non-specific and which provided no spatial cues, had a positive effect on postural stability by decreasing postural sway. Suppressing visual information has a greater negative impact on postural sway, which was not compensated for by the positive auditory suppression effect, to which patients with AD were significantly more vulnerable. Auditory information, albeit less significant than vision, appears to not be a negligible factor in the control of posture in everyday environmental scenarios and challenges. This is particularly relevant in patients with AD who, even when the peripheral sensory system is intact, have impaired central processing and demonstrate re-weighting of sensory dependence. To the best of our knowledge this is the first study evaluating the influence of the auditory system on postural sway in AD. Future studies should investigate the potential application of auditory feedback sensory information, particularly while performing conflicting or dual tasks, and/or in the presence of different sensory inputs within changing environments, on postural stability.

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Chapter 3.3.

Miguel F. Gago, Vitor Fernandes, Jaime Ferreira d, Hélder Silva, Maria L. Rodrigues, Luís Rocha, Estela Bicho and Nuno Sousa.

The effect of levodopa on postural stability evaluated by wearable inertial measurement units for idiopathic and vascular Parkinson's disease.

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The effect of levodopa on postural stability evaluated by wearable inertial measurement units for idiopathic and vascular Parkinson's disease

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ABSTRACT

Background: Postural stability analysis has shown that postural control is impaired in untreated idiopathic Parkinson's disease (IPD), even in the early stages of the disease. Vascular Parkinson's disease (VPD) lacks consensus clinical criteria or diagnostic tests. Moreover, the levodopa effect on postural balance remains undefined for IPD and even less so for VPD.
Objective: To characterize postural stability, using kinematic analysis with wearable inertial measurement units, in IPD and VPD patients without clinical PI, and to subsequently analyze the response to levodopa.
Methods: Ten patients with akinetic-rigid IPD and five patients with VPD were included. Clinical and postural stability kinematic analysis was performed before and after levodopa challenge, on different standing tasks: normal stance (NS), Romberg eyes open (REO) and Romberg eyes closed.
Results: In the "off state", VPD patients had higher mean distances and higher maximal distance of postural sway on NS and REO tasks, respectively. VPD patients maintained a higher range of anterior–posterior (AP) postural sway after levodopa. In the absence of PI and non-significant differences in UPDRS-III, a higher mPIGD score in the VPD patients was mainly due to gait disturbance. Gait disturbance, and not UPDRS-III, influenced the degree of postural sway response to levodopa for VPD patients.
Conclusion: Quantitative postural sway evaluation is useful in the investigation of Parkinsonian syndromes. VPD patients have higher AP postural sway that is correlated with their gait disturbance burden and also not responsive to levodopa. These observations corroborate the interconnection of postural control and locomotor networks.

1. Introduction

Postural control encompasses the acts of aligning the body with respect to gravity and maintaining, achieving or restoring the body center of mass (COM) relative to the base of support or, more generally, within the limits of stability during daily activities. Postural control is achieved by the complex integration and coordination of multiple body systems, including the vestibular, visual, auditory, motor, and higher level premotor systems [1], often unconsciously [2]. Postural instability (PI) is one of the most disabling features of idiopathic Parkinson's disease (IPD) and, generally, it is a manifestation of the late stages of the disease [3]. Yet, there is some evidence that postural control is already impaired in early stage of IPD without overt clinical PI [4]. Postural control can be characterized by the following four main postural control systems: (1) balance during quiet stance, (2) reactive

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postural adjustments to external perturbations, (3) anticipatory postural adjustments in preparation for voluntary movements, and (4) dynamic balance during movements, such as gait [5]. In this sense, postural control has a fundamental role in gait of establishing and maintaining appropriate postural orientation of body segments relative to each another and to the environment as well as to ensure dynamic stability of the moving body [6].

Vascular Parkinsonism (VPD) is a Parkinsonian syndrome that is typically characterized by lower body parkinsonism, marked gait difficulty, less tremor, less rigidity, better hand dexterity, relatively symmetrical symptomatic distribution, association with pyramidal tract signs, more frequent dementia, and poor response to levodopa treatment compared to IPD [7]. However, there are no consensus clinical criteria for VPD or its specific clinical features; additionally, there is a lack of diagnostic tests to differentiate VPD from IPD [8]. In terms of treatment, although it is recognized that the dopaminergic benefit tends to fade away with the progression of IPD, the objective effect of dopaminergic therapy on postural balance remains controversial for IPD and is even more questionable for VPD. There is increasing research to understand what and how networks of postural control and gait, both dopaminergic and non-dopaminergic, interact [9]. VPD, which is pathologically different from Parkinsonian syndrome but with clinical similarities to IPD [8], may serve as a good comparison model for investigating the postural stability on different and increasingly demanding postural and cognitive tasks and its response to levodopa.

Objective measures of balance using wearable inertial sensors are sensitive, specific and responsive to postural balance testing on clinical practice [10] and act as a diagnostic tool that is complementary to the traditional force plate measurements [4]. To characterize postural stability in IPD and VPD patients and to subsequently analyze the response to levodopa, we evaluated postural stability using kinematic analysis derived from wearable inertial measurement units on early disease akinetic-rigid IPD and VPD patients without clinical PI.

2. Materials and methods

2.1. Subjects and clinical assessment

Patients were consecutively recruited from our Movement Disorders outpatient consult, fulfilling criteria for IPD (UKPDS Brain Bank criteria) or VPD [8]. IPD and VPD patients had normal clinical postural stability measured by the retropulsion test (item 12 on MDS-UPDRS-III), and they had no dyskinesia. IPD patients had an Hoehn&Yahr of $\leq$2 (“off state”) and an akinetic-rigid profile. VPD patients predominantly presented with lower body Parkinsonism with independent but impaired gait; they were short stepped and stooped, which was related to an acute or chronic cerebrovascular disease, fulfilling the proposed criteria for VPD [8]. VPD patients had subcortical or basal ganglia focal lesions without large vessels stroke that were qualitatively classified from the neuroradiologist's reports. Patients were considered as being on their best “on” dopaminergic regimen in the three previous months. The exclusion criteria were dementia, orthopedic, musculoskeletal, vestibular disorder, significant visual or auditory deficit, and alcohol abuse. VPD patients with motor deficits, whether related to stroke or not, were also excluded.

Age has been associated with kinetic performance for postural stability [11]. Therefore, VPD and IPD age-matched patients were included. The collected variables consisted of demographic (gender, age, and education) and biometric data reported as influencing kinetic performance, such as weight, height, body mass index. The center of mass (COM) was determined at 55% of a patient's height above the ground [12]. Clinical data were also collected, including years of disease duration; Movement Disorder Society-Unified Parkinson's Disease Rating Scale III (MDS-UPDRS III) (scored as either an on “off” or on “on” state); Levodopa Equivalent Levodopa Daily Dose [13]; Levodopa suprathreshold challenge dose; and motor benefit (percentage of the difference between “off” and “on” states). The modified Postural Instability Gait Disorder (PIGD) score part III was derived from the sum of MDS-UPDRS items (3.9 (arising from chair), 3.10 (gait), 3.11 (freezing of gait), 3.12 (postural stability), 3.13 (posture), and 3.14 (global spontaneity of movement)) [14]. A brief neuropsychological examination was performed using the Portuguese version of the Montreal Cognitive Assessment test (MoCA) with scores normalized to the Portuguese population [15] no more than 1 month prior to the kinetic assessment. The levels of education were categorized by years of schooling as follows: 0 (analphabetic), 1 (1–4 years), 2 (5–9 years), 3 (10–12 years), and 4 ($>$12 years). The study protocol derived from the ICVS-3Bs and the Algoritmi Center and was approved by hospital local ethics committee. Written informed consent was received from all participants in the study.

2.2. Kinematic postural tasks

Five kinetic sensing modules, harboring an 8051 microprocessor embedded in CC2530 *Texas Instrument* SoC (System on Chip), and a wearable inertial measurement unit MPU6000 (tri-axial accelerometer and gyroscope) [16] operating with a sample rate frequency of 113 Hz on a SD card were attached to the following five body segments: trunk (on the COM); both legs (middle of ankle-knee) and both thighs (middle of knee-iliac crest) by Velcro bands. Video capture (sample rate of 60 fps) and data logging were synchronized by a bidirectional radio signal transmission through a USB coordinator node connected to a PC with custom designed Matlab© software.

Our methodology and mathematical formulas for kinematic acquisition have been previously published [17]. We focused on some kinematic measurements that were derived from the wearable sensor unit placed at the COM, including the total length of sway (cm); maximal and mean distance of sway (cm) with respect to the origin; maximal linear velocity (cm/s); and range of medial-lateral (ML) and anterior–posterior (AP) sway (cm) (on the *X* and *Y* axis transverse planes, respectively). As one of the human's mechanisms of maintaining balance is to vary the height and COM by bending the knees and trunk, kinematic data was constantly adjusted to real height adjusted from the wearable sensor units placed on the shanks and thighs.

Subjects were instructed to perform the following three different tasks, first in the “off” and then in the “on state”: normal comfortable standing, Romberg test with eyes open, and Romberg with eyes closed. Patients were clinically and kinematically evaluated in the “off state”, in the morning, after a 12-h period without any dopaminergic medication. Afterwards, they were given a suprathreshold dopaminergic medication of 150% of their usual morning dose and were re-examined 90 min later regardless of the intensity of their subjective response.

Subjects performed the Romberg test barefoot with the medial aspects of the feet touching each other. During the tasks, subjects stood quietly with their arms hanging at their sides and their head in a normal forward-looking eye position directed to an object placed at 2 m away. All tasks were explained, and subjects had the chance to train before the definitive trial. Each task was performed for 30 s; during that time, the kinematic data were recorded. The trial was invalidated and started again if subjects moved any part of their body, spoke, opened their eyes for visual aid or performed a corrective step.

2.3. Statistical analysis

Gender comparisons were analyzed by the χ^2 Fisher exact test. Given the small number of subjects, statistical analysis was carried

out with a non-parametric exact test, the Mann–Whitney test (comparison between groups), and by a Wilcoxon matched pair test for the magnitude of change (intragroup) after levodopa challenge and for the effect of the visual suppression effect. Intragroup correlation of the basal ("off state") mPIGD score and the total MDS-UPDRS III score with a change in postural sway variables after levodopa challenge was evaluated with the Spearman test. Statistical analyses were conducted with software (SPSS 20.0) using a 95% level of significance.

3. Results

Five patients with VPD and ten patients with IPD were included. Thirteen patients fulfilling the criteria for VPD were excluded due to dementia (seven patients) and/or motor deficit and/or orthopedic problems (six patients). The demographic and anthropometric characteristics of the two groups are summarized in Table 1.

All VPD patients were males, but gender has not been described to influence postural sway [18]. Groups did not differ in age or anthropometric characteristics. Additionally, baseline clinical characteristics (years of disease duration, "off state" MDS-UPDRS III score, Equivalent Levodopa Daily Dose; Levodopa challenge dose; and Motor Benefit) were not significantly different between groups. VPD patients had a higher mPIGD score 8 [5,10], ($U = 4.0$; $z = -2.602$; $p = 0.006$) due essentially to a higher score on posture and gait. After levodopa challenge, both groups differed significantly on the MDS-UPDRS III ($U = 0.0$; $z = -3.062$; $p = 0.001$)) and mPIGD score ($U = 1.5$; $z = -2.907$; $p = 0.002$), reflecting, as expected, a lower motor benefit of levodopa for patients with VPD ($U = 0.0$; $z = -3.067$; $p = 0.001$).

Concerning postural sway analysis (Table 2, Fig. 1), we observed that in both groups, the requirement for postural control increased for the different tasks. This was evident in the higher values of total sway length and distance of sway in the ML and AP planes.

On "off state", in the normal stance, VPD patients had a higher mean distance of sway ($U = 7.0$; $z = -2.205$; $p = 0.028$), and on the REO task, they had a higher maximal distance ($U = 8.0$; $z = -2.08$; $p = 0.04$) and higher range of anterior–posterior sway ($U = 8.0$; $z = -2.082$; $p = 0.04$). In the "on state," VPD patients on the REO task also had a higher range of anterior–posterior sway ($U = 5.0$; $z = -2.449$; $p = 0.013$). Of note, in the "on state," there were no significant differences in the distance of sway between the two groups.

In intragroup analysis of the levodopa effect, only IPD patients had significant changes in the normal stance task. The total length (IPD: 6.07 [−5.98, 10.81]; VPD: 1.05 [−7.39, 7.39]) ($z = -2.191$, $p = 0.027$), maximal distance (IPD: 0.65 [−0.18, 2.57]; VPD: 0.14 [−2.63, 1.18]) ($z = -2.497$, $p = 0.01$), range of ML (IPD: 0.63 [−0.01, 2.03]; VPD: 1.19[−1.18, 1.88]) ($z = -2.701$, $p = 0.04$) and AP sway (IPD: 0.64 [−0.73, 2.15]; VPD: −0.17 [−5.11,1.15])($z = -1.988$; $p = 0.049$) were significantly increased in only the IPD group. When analyzing the effect of visual suppression, only IPD patients, and only in the "off state", registered a significant effect, and there was an increase in the total length ($z = -2.191$, $p = 0.027$) and maximal distance of sway ($z = -1.988$, $p = 0.049$). For the IPD group, there were no significant correlations in the basal mPIGD score ("off state") with the change in postural sway variables after levodopa challenge. In contrast, VPD patients had a significant correlation between the basal mPIGD score (OFF state) and the total length of sway in normal stance (rho = −0.949, $p = 0.014$) and range of AP sway on the REC task (rho = 0.9, $p = 0.037$). The basal MDS-UPDRS-III total score ("off state") had no significant correlation with any of the postural sway variables in either group.

Table 1
Demographics, anthropometric and clinical variables in idiopathic Parkinson's disease and vascular Parkinson's disease patients.

	IPD ($n = 10$)	VPD ($n = 5$)	Inter-group comparison
Gender (female/male)	6/4	0/5	*$p = 0.044$
Age	73 [61,79]	77 [63, 84]	$U = 18.0$; $z = -0.086$; $p = 0.418$
Height (m)	1.61 [1.52, 1.71]	1.61 [1.55, 1.68]	$U = 24.5$; $z = -0.062$; $p = 0.981$
Weight (kg)	73.2 [55, 85]	76.5 [68, 89]	$U = 15$; $z = -1.225$; $p = 0.254$
Body Mass Index (kg/m^2)	29 [24, 32]	31 [27, 34]	$U = 11.5$; $z = -1.673$; $p = 0.098$
Center of mass (cm)	88.3 [84, 94]	88 [85, 92]	$U = 24.5$; $z = -0.062$; $p = 0.981$
Level of Education	1 [1, 4]	1 [1, 1]	$\chi^2 = 2.359$; $p = 0.267$
MOCA	23 [16, 30]	12 [10, 15]	$U = 0.0$; $z = -3.067$; $p = 0.001$
Disease duration in years	6 [5, 10]	5 [3, 9]	$U = 25.0$; $z = -0.0$; $p = 1.0$
MDS-UPDRS III Off stage	30 [16, 53]	44 [33, 57]	$U = 10.0$; $z = -1.839$; $p = 0.075$
mPIGD off stage	3 [1, 7]	8 [5, 10]	*$U = 4.0$; $z = -2.602$; $p = 0.006$
Arising from chair	0 [0, 1]	1 [0, 2]	$p = 0.059$*
Gait	0 [0, 2]	2 [1, 2]	$p = 0.005$*
Freezing of gait	0 [0, 0]	0 [0, 0]	$p = 1.0$
Postural stability	0 [0, 0]	0 [0, 0]	$p = 1.0$
Posture	1 [0, 3]	3 [1, 3]	$p = 0.067$
Global spontaneity of movement	2 [0, 3]	2 [2, 3]	$p = 0.114$
MDS-UPDRS III On stage	13.5 [1, 24]	39 [26, 46]	*$U = 0.0$; $z = -3.062$; $p = 0.001$
mPIGD on stage	2 [0, 6]	7 [5, 8]	*$U = 1.5$; $z = -2.907$; $p = 0.002$
Arising from chair	0 [0, 1]	1 [0, 2]	$p = 0.032$*
Gait	0 [0, 0]	1 [1, 2]	$p = 0.001$*
Freezing of gait	0 [0, 0]	0 [0, 0]	$p = 1.0$
Postural stability	0 [0, 0]	0 [0, 0]	$p = 1.0$
Posture	1 [0, 3]	2 [1, 3]	$p = 0.121$
Global spontaneity of movement	1 [0, 2]	2 [1, 3]	$p = 0.017$*
Levodopa equivalent daily dose	685 [300, 1532]	750 [500, 1124]	$U = 24$; $z = -0.123$; $p = 0.931$
Levodopa challenge dose	300 [150, 400]	350 [200, 400]	$U = 18.5$; $z = -0.82$; $p = 0.458$
Motor benefit (%)	57.5 [47, 94]	19 [11, 26]	*$U = 0.0$; $z = -3.067$; $p = 0.001$

Data is presented as median [minimum, maximum].
IPD—idiopathic Parkinson's disease; VPD—vascular Parkinson's disease; COM–55% of individual's height; mPIGD—modified postural instability and gait disorder score (mPIGD) derived from the sum of the MDS-UPDRS items (arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity of movement).
* Significant at exact Fisher test.

Table 2
Postural kinematic variables on different postural tasks in idiopathic Parkinson's disease and vascular Parkinson's disease.

Kinematic variables	Normal stance			Romberg test with eyes open (REO)			Romberg test with eyes closed (REC)			REO vs. REC off stage	REO vs. REC on stage
	Off stage	On stage	*p*-Value[a]	Off stage	On stage	*p*-Value[a]	Off stage	On stage[a]	*p*-Value[a]	*p*-Value[a]	*p*-Value[a]
Total length of sway (cm)											
IPD	13.4 [8.3, 21.1]	19.4 [12.8, 25.4]	$p=0.027^{*}$	21.0 [10.5, 36.8]	22.1 [8.9, 32.8]	$p=0.922$	24 [13.8, 39.6]	23.2 [12.5, 47.2]	$p=0.846$	$p=0.027^{*}$	$p=0.064$
VPD	13.7 [12.8, 41.2]	20.2 [10.3, 33.9]	$p=1.0$	20.9 [18.7, 35.7]	21.3 [16.0, 50.0]	$p=0.31$	21.8 [14.4, 38.4]	23.3 [16.2, 57.3]	$p=0.313$	$p=0.625$	$p=0.625$
p-Value[b]	$p=0.254$	$p=0.953$		$p=0.679$	$p=0.513$		$p=0.953$	$p=0.768$			
Maximal distance of sway (cm)											
IPD	1.56 [0.92, 2.93]	2.46 [1.60, 3.55]	$p=0.01^{*}$	2.04 [1.36, 3.66]	2.5 [1.4, 4.3]	$p=0.23$	2.43 [1.46, 4.70]	2.43 [1.13, 8.4]	$p=0.625$	$p=0.049^{*}$	$p=0.695$
VPD	1.82 [1.46, 6.50]	3.0 [1.8, 4.0]	$p=0.81$	3.7 [1.9, 9.2]	3.2 [2.0, 5.9]	$p=0.81$	2.4 [1.64, 6.25]	3.26 [1.8, 5.4]	$p=0.625$	$p=0.188$	$p=0.438$
p-Value[b]	$p=0.206$	$p=0.440$		$p=0.04^{*}$	$p=0.129$		$p=0.953$	$p=0.594$			
Mean distance of sway (cm)											
IPD	0.57 [0.45, 1.32]	1.03 [0.42,1.98]	p=.084	1.15 [0.71, 2.04]	1.2 [0.65, 2.24]	$p=0.492$	1.17 [0.48, 2.79]	1.22 [0.53, 4.18]	$p=0.432$	$p=0.57$	$p=0.77$
VPD	1.15 [0.61, 2.50]	0.98 [0.5, 2.6]	$p=0.623$	1.8 [0.78, 4.3]	1.6 [0.82, 2.5]	$p=0.081$	1.1 [0.7, 2.3]	1.64 [0.8, 3.2]	$p=0.438$	$p=0.313$	$p=0.625$
p-Value[b]	$p=0.028^{*}$	p=.953		$p=0.129$	$p=0.165$		$p=0.679$	$p=0.513$			
Maximal linear velocity (cm/s)											
IPD	0.85 [0.22, 2.78]	1.3 [0.24, 1.77]	$p=0.43$	0.6 [0.28,2.6]	1.27 [0.37, 1.82]	$p=0.275$	0.65 [0.43, 2.9]	1.64 [0.46, 3.72]	$p=0.064$	$p=0.275$	$p=0.084$
VPD	0.79 [0.5, 7.20]	1.5 [0.5, 8.2]	$p=0.43$	1.46 [0.58, 2.8]	2.2 [0.41, 5.5]	$p=0.188$	1.48 [0.17, 3.8]	1.1 [0.06, 5.7]	$p=0.813$	$p=1.0$	$p=0.31$
p-Value[b]	$p=0.371$	$p=0.59$		$p=0.679$	$p=0.055$		$p=0.254$	$p=0.859$			
Range of ML sway (cm)											
IPD	0.8 [0.33, 3.4]	1.82 [0.86, 3.96]	$p=0.004^{*}$	2.68 [1.64, 5.29]	2.03 [1.04, 5.39]	$p=0.275$	2.49 [1.33, 5.47]	2.28 [1.23, 7.3]	$p=0.695$	$p=0.625$	$p=0.105$
VPD	1.75 [0.67, 2.0]	2.38 [0.36, 3.63]	$p=0.188$	2.4 [1.76, 3.20]	3.24 [2.38, 3.72]	$p=0.063$	2.4 [1.9, 2.5]	2.4 [1.8, 5.9]	$p=0.625$	$p=1.0$	$p=1.0$
p-Value[b]	$p=0.165$	$p=0.44$		$p=0.679$	$p=0.129$		p=.768	$p=0.768$			
Range of AP sway (cm)											
IPD	1.96 [0.99, 2.70]	2.86 [1.89, 3.78]	$p=0.049^{*}$	2.32 [1.3, 3.87]	2.45 [0.9, 4.2]	$p=0.77$	2.24 [1.77, 3.85]	2.04 [1.30, 4.40]	$p=0.492$	$p=0.557$	$p=1.0$
VPD	2.5 [1.6, 12.0]	2.74 [2.16, 6.9]	$p=0.625$	4.14 [1.75, 9.96]	5.3 [2.7, 10.9]	$p=0.125$	3.0 [1.7, 6.2]	3.3 [2.2, 7.3]	$p=1.0$	$p=0.18$	$p=0.063$
p-Value[b]	$p=0.371$	$p=0.44$		$p=0.04^{*}$	$p=0.013^{*}$		$p=0.371$	$p=0.055$			

Data is presented as median [minimum, maximum]. IPD—idiopathic Parkinson's disease; VPD—vascular Parkinson's disease; ML—medial-lateral; AP—anterior–posterior.
[a] Wilcoxon statistical analysis (intragroup analysis).
[b] Mann–Whitney statistical analysis (intergroup analysis).
[*] Significant at exact Fisher test.

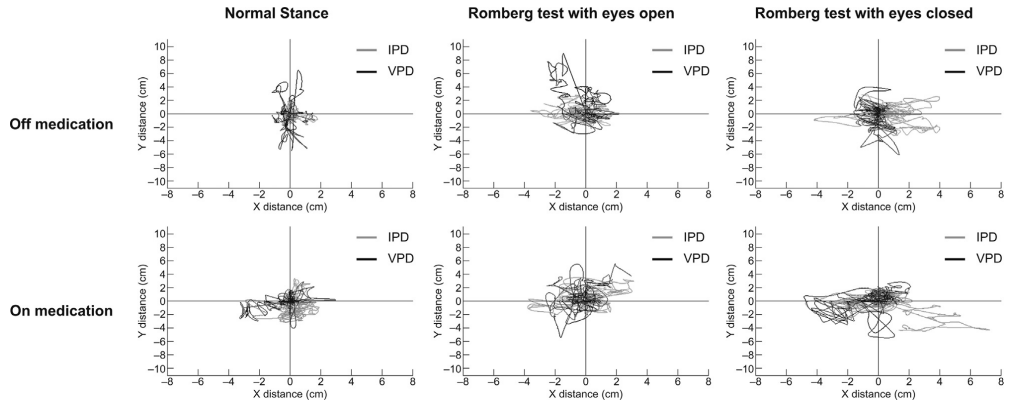

Fig. 1. Displacement on *x*-axis (medial-lateral) and *y*-axis (anterior–posterior) of inertial measurement unit on center of mass (55% of Height), plotted on different conditions (before (off) and after levodopa challenge (on)), for all subjects (idiopathic Parkinson's disease (IPD); vascular Parkinson's disease (VPD) patients).

4. Discussion

The present results indicated subclinical differences in postural sway between VPD and AR-IPD patients. This finding is in agreement with clinical evidence, diagnostic criteria and the different etiopathology of these two entities [8]. In agreement with the data from previous force platforms and IMU studies, we also found a significant increase in the displacement of sway from the origin after levodopa [19]. This is relevant because the role attributed to levodopa on postural control in IPD remains unclear due to conflicting results. Herein, we also demonstrate that levodopa only had a significant effect on IPD but not on VPD. Sway in patients with IPD who are in the "on state" are larger and faster than when in the "off state", which is perhaps because levodopa reduces the rigidity without improving control of posture or because subclinical dyskinesia increases body motion [20]. Additionally, the decrease in sway after dopaminergic medication has been correlated with a smaller risk of falling, whereas no change or increased postural sway correlated with higher risk [21]. In our study, levodopa did not have a positive effect on the range of the AP postural sway in VPD patients. Interestingly, the main difference between IPD and VPD was in the AP sway measures both in the "off" and "on" states. AP sway involves the inverted pendulum and ankle muscle sway strategy of postural control, which may be less affected in IPD than in VPD.

The etiology of the postural misalignment and flexed posture in IPD is not clear, but background muscle tone is larger, especially in flexor muscles. In spite of their forward inclination in the upright posture, IPD patients tend to fall backwards very easily, with both axial rigidity and poor trunk coordination contributing to the poor stability of IPD patients in response to backward body sway [22]. The more flexed posture of VPD patients, demonstrated in their mPIGD scores, may have contributed, but the larger AP range of sway can also represent a distinctive variable of VPD and higher risk of falling even without overt clinical PI.

More demanding postural control tasks, such as the Romberg under visual suppression, may have put our patients on higher cognitive alert and effort to control COM under stable limits. This may have attenuated the subclinical dyskinesia and increased postural sway that was only observed in the normal relaxed stance. Visual suppression increases the postural instability, making the patient more dependent on other systems, including the vestibular, proprioceptive inputs and postural controls nucleus such as the pedunculopontine nucleus [5]. We observed a significant effect of visual suppression on the postural sway of our IPD patients, which is concordant with other studies on early stage IPD [19]. This vulnerability was only present for IPD patients, which was evident in the "off state" and showed a positive response to levodopa, as previously reported [19]; importantly, we failed to find a positive response in VPD patients.

Increasing evidence suggests an important role of cognitive factors, such as executive function and attention, in the control of balance during standing and walking [23,24]. Many studies have shown that gait in IPD is more dependent on focused attention and external cues and that the frontal cortex may play a crucial role in controlling gait patterns [14]. The disruption of the microstructural organization of the frontal lobe white matter has been associated with the severity of VPD, reinforcing the hypothesis of the frontal lobe disconnection for gait problems and that the involvement of fibers related to the prefrontal cortex is crucial for the core features of VPD. In this respect, we cannot exclude that some findings in VPD patients can also be explained by their lower cognitive performance (lower values on MoCa), albeit without the criteria of dementia.

In the absence of clinical postural instability, the higher mPIGD score in both groups was mainly due to gait disturbance, especially prevalent in the VPD patients. After levodopa challenge, VPD patients had a higher basal mPIGD basal score, which is correlated with the lower total length postural sway change in normal stance; interestingly, this lower sway apparently persisted in the AP plane. In most cases of VPD, gait and postural stability are simultaneously impaired [25]. In this particular cohort of VPD patients, in the absence of clinically assessed postural instability, gait impairment influenced the degree of the postural sway response to levodopa. Locomotor generators and postural control are interconnected [26], and if postural control is still modulated by dopamine at least in the early stages of IPD without PI, this was not evident in VPD. Unlike for mPIGD, the UPDRS-IIII total score did not influence the postural sway response after levodopa challenge. A pure mechanical process, with less rigidity after levodopa influencing postural sway, is not the sole explanation for this; central postural control circuits, both dopaminergic and non-dopaminergic, could be involved [27].

4.1. Study limitations

It is important to note that we opted to include only the akynetic-rigid IPD subtype and age-matched VPD patients.

Therefore, our methodological concerns about the purity and homogenization of the VPD and IPD groups, excluding variables with potential bias on postural control, such as neuromuscular, osteoarticular and motor deficits, although theoretically a strength, led to the exclusion of a significant number of patients encountered in clinical practice. The small clinical sample of VPD patients limits the statistical inferences of comparison between groups. This difficulty in including a large number of VPD patients affects clinical cross-sectional studies [28]. Our evaluation of cerebrovascular disorder on brain MRI was merely qualitative. However, there is still no specific abnormal structural imaging pattern for VPD [25], and the terminology and definitions of the imaging features of cerebral small vessel disease vary widely, although recent advances have attempted to address this problem [29]. Nevertheless, quantitative analysis of the impact of the cerebrovascular system on brain MRI has been correlated with the severity of VPD [14]. Additionally, the volume of parietal white matter lesions has been associated with the MoCA score in VPD patients [30].

5. Conclusion

The results of our pilot study suggest that a quantitative postural sway evaluation is a useful tool for investigating the levodopa effect on Parkinsonian syndromes. VPD patients have higher AP postural sway, which is correlated with the gait clinical burden, and not responsive to levodopa. These observations corroborate the interconnection of postural control and locomotor networks, especially the non-dopaminergic ones.

Further studies with larger sample sizes that use less restrictive inclusion criteria and perform multivariate analyses are needed to determine the effect of the dopaminergic system and cognition on postural stability. Investigation should also be extended to patients with postural instability, monitoring the progression to more advanced stages of IPD, different profiles of VPD patients and even other Parkinsonian disorders, and a future study should include a correlation with a quantitative gait analysis.

Conflict of interest statement

There are no conflicts of interest to report.

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Chapter 3.4.

Darya Yelshyna, **Miguel F. Gago**, Estela Bicho, Vítor Fernandes, Nuno F. Gago, Luís Costa, Hélder Silva, Maria Lurdes Rodrigues, Luís Rocha and Nuno Sousa.

Compensatory postural adjustments in Parkinson's disease assessed via a virtual reality environment.

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Research report

Compensatory postural adjustments in Parkinson's disease assessed via a virtual reality environment

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HIGHLIGHTS

- Virtual reality allows the analysis of compensatory postural adjustments (CPA).
- IPD patients are highly susceptible to visually induced destabilization.
- CPA is modulated by mechanisms related to different time scales.
- Levodopa treatment increases the stabilizing effect by means of low frequencies CPA.

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ABSTRACT

Postural control is a complex dynamic mechanism, which integrates information from visual, vestibular and somatosensory systems. Idiopathic Parkinson's disease (IPD) patients are unable to produce appropriate reflexive responses to changing environmental conditions. Still, it is controversial what is due to voluntary or involuntary postural control, even less what is the effect of levodopa. We aimed to evaluate compensatory postural adjustments (CPA), with kinematic and time-frequency analyzes, and further understand the role of dopaminergic medication on these processes. 19 healthy subjects (Controls) and 15 idiopathic Parkinson's disease (IPD) patients in the OFF and ON medication states, wearing IMUs, were submitted to a virtual reality scenario with visual downward displacements on a staircase. We also hypothesized if CPA would involve mechanisms occurring in distinct time scales. We subsequently analyzed postural adjustments on two frequency bands: low components between 0.3 and 1.5 Hz (LB), and high components between 1.5 and 3.5 Hz (HB). Vertical acceleration demonstrated a greater power for discriminating IPD patients from healthy subjects. Visual perturbation significantly increased the power of the HB in all groups, being particularly more evident in the OFF state. Levodopa significantly increased their basal power taking place on the LB. However, controls and IPD patients in the ON state revealed a similar trend of the control mechanism. Results indicate an improvement in muscular stiffness provided by levodopa. They also suggest the role of different compensatory postural adjustment patterns, with LB being related to inertial properties of the oscillating mass and HB representing reactions to the ongoing visual input-changing scenario.

1. Introduction

Postural control is a complex dynamic mechanism, which integrates information from visual, vestibular and somatosensory systems, with the central nervous system (brain and spinal cord) adapted to the musculoskeletal system status (muscles, bones, tendons and ligaments). Even during quiet standing, beside the mechanical antero-posterior, ankle strategy, and the medial-lateral hip strategy, the center of mass (COM) is also continuously controlled by a central nervous system (CNS) time-delayed feedback loop, in reaction to predictable and unpredictabe postural perturbations [1]. Anticipatory (APA) and compensatory postural adjustment (CPA) strategies are the two main mechanisms used

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by the CNS in order to deal with body perturbations that may either be internally generated (e.g., self-initiated movements) or externally generated (e.g., being pushed at shoulder level while walking) [2]. When postural perturbation is unpredictable, postural muscles are activated to restore stability after the moment of perturbation. These later responses (CPA) are triggered by sensory feedback signals and help in dealing with the actual effects of a perturbation [3,4]. While APA are observed only in the case of predictable perturbations, CPA are seen during both, predictable (following APA) and unpredictable perturbations. Often CPA are of larger magnitude in response to unpredictable perturbations [5].

The body schema is a perception of one's body in space and body parts associated with movement and is influenced by visuomotor processing. The temporoparietal cortex, including the posterior parietal cortex and the vestibular cortex, appears to integrate real-time signals in the visual, proprioceptive, and vestibular sensations so that the body schema can be always updated. [6]. Absence or degradation of any type of sensory input may affect balance performance. The latter is commonly observed with aging, leading to increased instability, falls and consequent injuries [7–9]. Disorders such as Idiopathic Parkinson Disease (IPD) further aggravate balance disturbances of elderly population [10,11]. Deficiency in the information processing from the temporoparietal cortex to the frontal cortex may cause errors in APA, CPA and gait difficulties, such as the "freezing of gait" [6].

Postural control is compromised in subjects with untreated IPD due to disturbed postural reflexes, poor control of voluntary movements, orthostatic hypotension and side effects of certain medications that include dyskinesia [12]. Compared to healthy elderly adults, IPD patients are unable to produce appropriate reflexive responses to changing environmental conditions. In IPD, besides motor deficits contribution, postural impairment is also associated with abnormal spatial and temporal processing of sensory information, producing incorrect signals for the preparation and execution of voluntary movement [11,13]. It has been established that APA and CPA are compromised in IPD, with patients not only having difficulty switching between postural strategies, but also being unable to appropriately scale the size of their postural responses to the size of environmental change [14–17]. Discrepancies of reports, with IPD patients presenting larger or decreased sway, are probably due to differences in voluntary and involuntary posture postural control and/or study design [18]. Moreover, effects of levodopa treatment are controversial. Some studies found a worsening of sway abnormalities in view of increased sway area and reduced mean velocity [19,20], while others report a larger and a faster sway [21,22]. Regarding CPAs, levodopa has been reported not to improve slower CPAs on IPD patients and theirs difficulty in using cognitive set to modify responses to surface perturbations [15]. In fact, levodopa therapy can compromise the immediate postural adaptation and refinement of postural strategy, changes in amplitude of vertical ground reaction forces and forces applied to support apparatus within conditions between the initial and final trials, that is present on the OFF state and on healthy subjects [23].

In the last years, the impact of visual perturbation on postural adjustments has been widely explored. Visual deprivation during quiet stance eliminates one of the inputs to the control mechanism, producing a destabilizing effect. This process results in an increasing need for postural adjustments, affecting in a larger scale elderly impaired subjects [8,24,25] Susceptibility to visual stimulation has been studied in several conditions, such as visual focus on differently distanced targets [26] or exposal to a moving surround, which in most recent researches, was implemented through an immersive virtual scene allowing for a better perception of the induced motion. This virtual reality creates an illusion that puts the subject in a different place other than where she/he physically is [27]. Besides inducing self-motion illusion, moving visual surround conflicts with perceptions from somatosensory and vestibular systems, since the body has not actually moved. As a consequence, the body generates CPA in the direction of the visual perturbation [28,29].

Balance integrity is most commonly assessed by kinetic and kinematic analyzes [30]. Estimates of center of pressure (COP) trajectory derived from force platforms have been extensively used to compute stationary sway measures, presented in time and frequency domains [7]. Recently, accelerometry emerged as an alternative technique to posturography, successfully exploiting the same measures with the advantages of lower cost, reduced size and portability. Inertial Measurement Units (IMUs), which include both accelerometers and gyroscopes, provide additional information about body tilt and orientation [31,32]. Stationary signal analysis provides insightful information regarding the postural control. However, it has long been demonstrated that this system is dynamically regulated [33]. An appropriate non-stationary technique should be employed to characterize the existing spectral variations, such as time-frequency analysis [34] . Interestingly, numerous studies have also reported that these changes occur in two distinct time scales: a fast (high frequency) open-loop control and a slower (low frequency) corrective feedback-based control [1,35].

The primary objective of this research is to evaluate visually induced CPA in a changing virtual reality scenario, in healthy subjects (controls) and IPD patients, by means of kinematic and time-frequency analyzes of IMU records. As a second objective, we aim to understand the role of dopaminergic medication on postural adjustment mechanisms.

2. Methodology

2.1. Subjects and clinical assessment

The study protocol was derived from the ICVS-3Bs and the Algoritmi Center and was approved by the hospital local ethics committee. Written informed consent was received from all participants in the study. 15 patients and 19 controls were consecutively recruited from our Movement Disorders outpatient consult, fulfilling criteria for IPD (UKPDS Brain Bank criteria). IPD patients had normal clinical postural stability measured by the retropulsion test (item 12 on MDS-UPDRS-III), had an Hoehn &Yahr of 2 (OFF state). The exclusion criteria were dementia, orthopedic, musculoskeletal, vestibular disorder, significant auditory deficit, and alcohol abuse. Patients had no somatosensory deficit, on neurological examination, nor wore glasses or contact lens to correct vision. The collected variables consisted of demographic (gender, age, and education) and biometric data reported as influencing kinetic performance, such as weight, height, body mass index. Clinical data were also collected, including years of disease duration, Movement Disorder Society-Unified Parkinson's disease rating scale III (MDS-UPDRS III) (scored as either an in the OFF or in the ON state), levodopa equivalent daily dose [36], and morning levodopa challenge dose. A brief neuropsychological examination was performed using the Portuguese version of the Montreal Cognitive Assessment test (MoCA) with scores normalized to the Portuguese population [37] no more than 1 month prior to the kinetic assessment. The levels of education were categorized by years of schooling as follows: 0 (analphabetic), 1 (1–4 years), 2 (5–9 years), 3 (10–12 years), and 4 (>12 years).

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2.2. Apparatus and postural tasks

One sensing module, harboring an 8051 microprocessor embedded in CC2530 Texas Instrument SoC (System on Chip), and a wearable inertial measurement unit MPU6000 (tri-axial accelerometer and gyroscope), operating with a sample rate frequency of 118 Hz on a SD card [38], was attached to the center of mass (COM), located at 55% of the patient's height above the ground.

The subjects were submitted to a realistic visual scene with three-dimensional depth information by wearing the Oculus Rift goggles – a virtual reality headset device with a 100° field-of-view. Tuscany Demo (Fig. 1) was chosen as the virtual scenario for performing unexpected visually induced motion on a staircase and evaluation of the response to the illusory perception of falling (translation down the stairs). While performing the tasks, the subjects were instructed to maintain still standing, barefoot, with the medial aspects of the feet touching each other, arms hanging at their sides and using a safety ceiling trunk belt. Subjects were instructed not to abandon this position and, if need be, to do a corrective adjustment by bending their knees. During the preparatory phase, subjects were asked to identify and search for several objects embedded in the VR setting (e.g., floor, roof, stairs, fireplace, chandelier, window and door). Visual focus and eye width settings were adjusted for each participant to display a clear stereoscopic 3-D image. Initially, the subjects stood at the top of the staircase in the virtual environment and were issued to focus their attention on the first stairs. Approximately ten seconds later, the scenario instantaneously moved down, creating a visual displacement, translating the subject to the middle of the stairs. After another 10 s, the scenario moved upwards, placing the subject back on the top of the stairs, until the next trial. After experimenting several translations, subjects were asked to explain if they felt that they were virtually pushed into the middle of the stairs, as they would have experienced in real life. This procedure was repeated several times with a minimum 20-s gap between trials and a minimum of 5 preparatory trials per subject, as to guarantee immersion into the virtual reality, to a maximum of 8 (in two patients), as assessed by subjects' answer to VR subjective immersion feeling. The neurologist was responsible for triggering the downward translation in a manual and random fashion, thus adverting adaptation and learning effect and putting individuals unaware of the exact moment of the upcoming event. A total of 5 effective "falling" trials per subject, 10 s duration, with the same methodology as in the preparatory phase, were selected as object of subsequent analysis. The translation in the virtual environment corresponds to approximately 1.17 meters of displacement along the vertical axis.

Patients were clinically and kinematically evaluated in the OFF state, and in the ON state after morning levodopa dose, on the same day. OFF state evaluation took place in the morning, after a 12 h period without any dopaminergic medication. Afterward, IPD patients were given their usual morning dose dopaminergic medication and were re-examined 90 min later regardless of motor response.

2.3. Data analysis

2.3.1. Kinematic analysis

IMUs allow for a more elaborate study of motor patterns than procedures relying solely on accelerometers or force platforms. Joining accelerometer and gyroscope information provides us with roll and pitch angles of body orientation, and a reasonable estimation of its position [39] .

No clear procedures have yet been established for accelerometer data processing, but the main energy content of human movement is held below 3.5 Hz [30,31] . For this reason, the raw acceleration signals were filtered with a zero-phase low-pass Butterworth filter with a 3.5 Hz cutoff frequency. Due to the abdominal placement of the sensor, acceleration signals went through additional high-pass filtering in order to eliminate interference that might be caused by the act of breathing. Considering a normal respiratory frequency in adults, i.e., 18 breaths per minute [40], we applied a zero-phase high-pass Butterworth filter with a 0.3 Hz cutoff frequency.

Another version of the accelerometer signal – one that takes into account lower frequency components – should be applied in order to characterize body orientation and approximate its displacement [24,32]. For this purpose, both the raw acceleration and gyroscope signals underwent zero-phase low-pass Butterworth filtering with 0.5 Hz and 2 Hz cutoff frequencies, respectively. Detailed explanation of the methodology used to obtain body orientation – pitch and roll angles – and estimate COM displacement can be found in our previous study [24].

In order to guarantee an equal level of sensory perturbation, we selected the last trial from each subject as being the most representative of the overall response to the visual motion. Kinematic measures were computed from 8 s time segments after the last onset of the visual down-moving stimulus. Table 2 contains time-domain features that characterize sway magnitude and variability.

2.3.2. Time-frequency analysis

Many real-world signals, such as postural adjustment recordings, are non-stationary, implying that their spectral content changes over time. This is especially true when trying to assess responses to a particular stimulus. Classical frequency representations based on Fourier transform cannot provide an accurate spectrum analysis, since they only reflect global frequency content without specifying when the changes occurred. The concept of time-frequency distributions (TFD) was introduced to circumvent this limitation, as functions in both time and frequency [41].

One of the first presented solutions implements an extension to traditional Fourier analysis: short-time Fourier transform (STFT). The STFT estimates the energy spectrum (spectrogram) using a sliding window, thus assuming local stationarity of the signal. The resulting spectrogram depends on window size, which is responsible for the trade-off between time and frequency resolutions. The bigger the window size, the better the frequency resolution and the ability to detect low-frequency components that are characteristic to postural adjustments. On the other hand, it sacrifices a large amount of time information, which is especially critical when analyzing short-duration signals. This is the major limitation of spectrograms, making them unsuitable for COM data analysis [34,42].

The minimum mean cross-entropy (MMCE) method solves this problem by combining information from several sources. Given a finite set of spectrograms computed with different window sizes, the resulting TFD is a much better approximation of the time-varying spectrum than any of these individual spectrograms. Investigations on the MMCE method pointed out its low computational demand and ability to closely approximate to positive TFDs of the Cohen-Posch class, which are the most appropriate for real-world signal analysis [43,44].

The majority of studies concerning postural adjustments evaluation using inertial sensors considered the vertical component of acceleration insignificant and restricted their analysis to the 2D plane – a common practice in posturography. If a vertical visual motion is evaluated, these data might not be able to properly reflect posture responses [27]. A study, which evaluated outputs from all accelerometers' axis to detect age-related changes in postural balance, detected a great sensitivity of the vertical component for distinguishing young from elderly subjects [45]. This interesting finding, along with the direction of our VR visual stimulus, and also the displacement occurring mainly on the z-axis (Table 2), led to the selection of vertical acceleration for time-frequency analysis.

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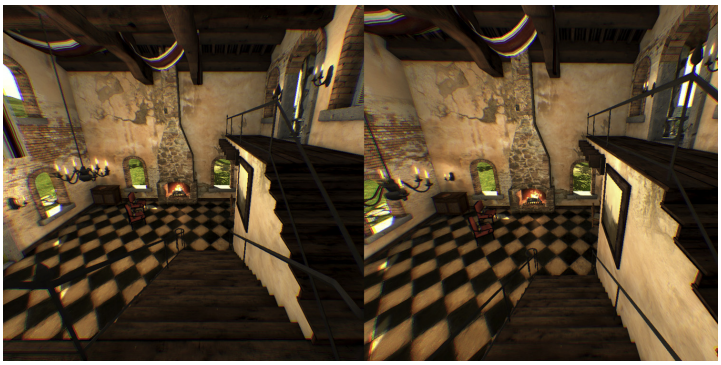

Fig. 1. Virtual environment created on the Oculus Rift, with the two translating scenarios: top of the staircase (left) and after a visual displacement of 1.17 meters along the vertical axis, translating to the middle of the stairs (right).

Table 1
Data is presented as median ± standard deviation, and mean [minimum, maximum] for level of education. Idiopathic Parkinson's disease (IPD); Movement Disorders Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS). Montreal Cognitive Assessment test (MoCA). Intergroup statistical comparison was performed with Mann–Whitnney test.

	Controls($n = 19$)	IPD($n = 15$)	Inter-group comparison
Gender (female/male)	8/11	9/6	$^{*}p = 0.491$
Age	69.9 ± 6.7	71.6 ± 8.1	$U = 123.5$; $z = -0.662$; $p = 0.519$
Weight (kg)	74.9 ± 12.6	73.5 ± 12.1	$U = 140$; $z = -0.087$; $p = 0.939$
Height (m)	1.63 ± 0.09	1.61 ± 1.0	$U = 124$; $z = -0.625$; $p = 0.542$
Body Mass Index (Kg/m2)	28.0 ± 2.6	28.1 ± 2.7	$U = 133$; $z = -0.330$; $p = 0.758$
Level of Education	1 [0, 2]	1 [0, 1]	$\chi^2 = 2.359$; $p = 0.456$
MoCA	24.2 ± 3.3	22.2 ± 3.7	$U = 95$; $z = -1.656$; $p = 0.10$
Disease duration (years)	.	5.3 ± 2.6	
MDS-UPDRS III Off stage	.	43.7 ± 15.0	
MDS-UPDRS III On stage	.	18.3 ± 9.5	
Levodopa Equivalent Daily Dose	.	1108 ± 434	
Levodopa morning dose	.	389 ± 178	
Motor Benefit (%)	.	59.1 ± 14.5	

Generally, a TFD by itself provides mainly descriptive information. A quantitative description of its dynamic behavior can be achieved by defining several time-dependent parameters: instantaneous average power (IAP), instantaneous mean frequency (IMF) and instantaneous bandwidth (IBW), also known as standard deviation of frequency content [46,47]. The IAP allows monitoring sudden changes due to postural adjustments. The IMF represents the overall frequency shift at each time.

After being downsampled to 10 Hz, the vertical acceleration assessed the dynamical properties of the CPAs. For each subject, we extracted time segments including all trials with a margin of 10 s prior to the first and after the last stimulus. Time-varying spectrum was estimated by an MMCE combination of spectrograms computed with Hanning windows of 15, 31 and 127 samples [43]. The Time-Frequency Toolbox (v1.2) for MATLAB© provided the function for MMCE computation.

On a subsequent analysis, we hypothesized that postural adjustments may involve mechanisms occurring in distinct time scales and thus two frequency bands were defined: a lower band containing components between 0.3 and 1.5 Hz (LB), and a higher band with components between 1.5 and 3.5 Hz (HB). A more precise evaluation of the visual destabilization is achieved when the subject is focused and unaware of the upcoming event. In order to identify this increased attentional demand during quiet stance, we computed the total power of the high-frequency band 4 s prior to the visual stimulus for all trials, and selected the one with the lowest value. All data processing and feature computation were performed with a custom-made MATLAB© code.

2.4. Statistical analysis

Gender comparisons were analyzed by the χ^2 Fisher exact test. Given the small number of subjects, the intergroup statistical analysis was carried out with a non-parametric Mann–Whitney exact test. Wilcoxon matched pair test was used for Control and IPD's intragroup changes, for separate band powers of TFD analysis, and for the evaluation of levodopa treatment. Statistical analyzes were conducted with software (SPSS 20.0) using a 95% level of significance.

3. Results

3.1. Subjects

Fifteen patients with IPD (6 women, 9 men) and nineteen controls (11 females/8 males) were included in this study. The demographic and anthropometric characteristics of the two groups are summarized in Table 1, as is the clinical characteristics of IPD patients. Groups were equally matched for demographic and anthropometric characteristics. IPD patients had a positive response to morning levodopa dose of 59.1% (mean), 14.5 (standard

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Table 2
Mann–Whitney *p*-values for comparison between controls (C) and Parkinson's disease patients, in the OFF state (IPD OFF), and after morning leovodopa dose, ON state (IPD ON). Significant *p*-values were shadowed. Standard deviation (SD); average acceleration magnitude (AAM).

	(Mean ± SD)			Intergroup comparison (*p*-value)		
Kinematic parameters	C	IPD OFF	IPD ON	C vs. IPD OFF	C vs. IPD ON	IPD OFF vs. IPD ON
SD velocity (cm/s)	0.634 ± 0.083	0.733 ± 0.379	0.799 ± 0.296	0.811	0.137	0.303
Maximum velocity (cm/s)	2.841 ± 0.385	3.357 ± 1.647	3.926 ± 1.697	0.681	0.023	0.095
SD velocity on X-axis (cm/s)	0.959 ± 0.172	0.991 ± 0.511	1.055 ± 0.305	0.537	0.372	0.330
Maximum velocity on X-axis (cm/s)	2.295 ± 0.442	2.322 ± 1.163	2.293 ± 0.633	0.190	0.918	0.679
SD velocity on Y-axis (cm/s)	0.829 ± 0.237	1.087 ± 0.584	1.219 ± 0.737	0.336	0.128	0.454
Maximum velocity on Y-axis (cm/s)	1.963 ± 0.691	2.668 ± 1.223	3.146 ± 2.090	0.128	0.060	0.359
Sway Path (cm)	9.016 ± 1.516	10.509 ± 5.039	11.828 ± 4.902	0.758	0.137	0.252
Sway Area (cm^2)	1.959 ± 0.919	3.747 ± 5.702	3.270 ± 2.556	0.271	0.451	0.934
Elliptic Area (cm^2)	4.918 ± 3.006	8.354 ± 12.223	7.363 ± 6.315	0.410	0.607	0.599
SD acceleration on X-axis (cm/s^2)	0.448 ± 0.091	0.428 ± 0.134	0.475 ± 0.183	0.410	0.973	0.359
Range acceleration on X-axis (cm/s^2)	2.432 ± 0.548	2.298 ± 0.665	2.423 ± 0.893	0.256	0.681	0.762
AAM acceleration on X-axis (cm/s^2)	0.346 ± 0.076	0.337 ± 0.114	0.380 ± 0.151	0.560	0.732	0.303
SD acceleration on Y-axis (cm/s^2)	0.391 ± 0.103	0.438 ± 0.172	0.472 ± 0.245	0.656	0.515	0.389
Range acceleration on Y-axis (cm/s^2)	2.092 ± 0.663	2.104 ± 0.789	2.340 ± 1.304	0.973	1.000	0.389
AAM acceleration on Y-axis (cm/s^2)	0.306 ± 0.084	0.349 ± 0.137	0.375 ± 0.196	0.471	0.451	0.389
SD acceleration on Z-axis (cm/s^2)	0.258 ± 0.070	0.384 ± 0.136	0.389 ± 0.179	0.002	0.023	0.890
Range acceleration on Z-axis (cm/s^2)	1.364 ± 0.456	2.002 ± 0.807	2.046 ± 0.948	0.021	0.030	0.890
AAM acceleration on Z-axis (cm/s^2)	0.203 ± 0.055	0.306 ± 0.103	0.308 ± 0.143	0.001	0.021	0.804

deviation). VR visual perturbation elicited no need for a corrective step on either group.

3.2. Kinematic features

Kinematic analysis revealed significant differences in velocity and acceleration between healthy subjects and IPD patients. No statistically significant changes in displacement-based measures were found between IPD patients in the ON and OFF states. Nevertheless, levodopa significantly increased the maximum velocity (C vs. IPD ON state ($U = 77.0$; $z = -2.27$; $p = 0.023$)), without a significant prevalence on either axis. The vertical acceleration signal demonstrated a greater power in discriminating IPD patients from Controls. IPD patients, either in the OFF or ON state, showed a significant increase in average acceleration magnitude (AAM) (C vs. IPD OFF: ($U = 50.0$; $z = -3.21$; $p = 0.001$); C vs. IPD ON: ($U = 76.0$; $z = -2.31$; $p = 0.021$)), standard deviation (SD) (C vs. IPD OFF: ($U = 54.0$; $z = -3.07$; $p = 0.002$); C vs. IPD ON: ($U = 77.0$; $z = -2.27$; $p = 0.023$)), and range of acceleration (C vs. IPD OFF: ($U = 76.0$; $z = -2.31$; $p = 0.021$); C vs. IPD ON: ($U = 80.0$; $z = -2.17$; $p = 0.03$)), on the z-axis (vertical) acceleration signal (Fig. 2).

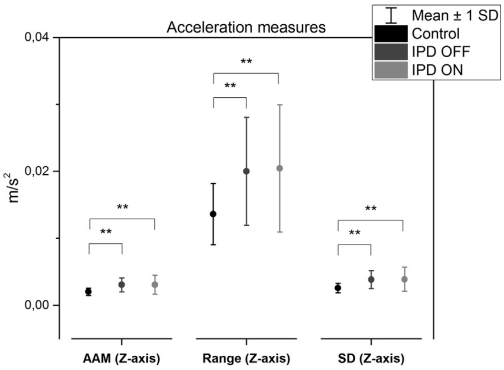

Fig. 2. Mean values of z-axis acceleration measures: average acceleration magnitude (AAM), range and standard deviation (SD) from healthy subjects (control) and IPD patients in the ON (IPD ON) and the OFF (IPD OFF) states. Brackets with two asterisks represent statistically significant ($p < 0.05$) results of intergroup Mann–Whitney test.

3.3. Time–frequency distributions

a) Instantaneous mean frequency (IMF)

TFD analysis reflected pronounced differences of the frequency patterns in response to visual perturbation, which were perceived at separate power bands level. Intergroup comparison revealed substantial divergence between Controls and IPD patients, on IMF and low and high power bands. Before the environment visual scenario change (−4–0 s interval) IPD in the ON state were shifted to lower IMF (Fig. 3; Table 3) (IPD ON vs. IPD OFF, $p = 0.001$). Immediately after and towards the end, IPD patients in the ON state tended for a higher IMF (C vs. IPD ON (0–4 s: $z = -2.029$, $p = 0.043$), (4–8 s: $z = -2.168$, $p = 0.030$)). Both Control and IPD in the ON state groups presented a monotonic increase in IMF along all considered time intervals (Fig. 3). In contrast, in the OFF state, IPD patients tended for lower IMF (4 to 8 s interval: C vs. IPD OFF, $p = 0.017$).

Concerning the intragroup analysis, a pronounced shift to higher frequencies was observed in healthy subjects during the last 4 s interval (−4–0 vs. 4–8 s: $z = -2.254$, $p = 0.023$). In contrast, IPD patients in the OFF state displayed a trend for lower frequencies after the visual perturbation (Fig. 3), which was mostly perceived at the last 4 s (−4–0 vs. 4–8 s: ($z = -2.158$, $p = 0.030$), 0–4 vs. 4–8 s; ($z = -1.988$, $p = 0.048$)).

- Lower band (LB) power

On the LB power, no differences were found between IPD patients in the OFF and ON states. However, OFF state IDP patients exhibited a significantly greater LB than healthy subjects in all of the considered time intervals (C vs. IPD OFF: (−4–0 s: $U = 75.0$; $z = -2.34$; $p = 0.019$) (0–4 s: $U = 53.0$; $z = -3.10$; $p = 0.001$) (4–8 s: $U = 45.0$; $z = -3.38$; $p < 0.001$)). Moreover, IPD patients in the ON state showed an even larger increase of LB power in comparison with the Control group (C vs. IPD ON (−4–0 s: $U = 82.0$; $z = -2.10$; $p = 0.036$) (0–4 s: $U = 84.0$; $z = 2.03$; $p = 0.043$) (4–8 s: $U = 72.0$; $z = -2.45$; $p = 0.014$)).

Of note, IPD patients in the ON state and healthy subjects shared the same trend of energy pattern (Fig. 4) in the LB. In contrast, in the OFF state, IPD patients showed an opposite trend, where LB power increased significantly during the post-stimulus condition

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Table 3
Descriptive table of instantaneous average power and frequency (mean ± 1 standard deviation) for Controls, Parkinsons' disease patients (OFF stage (IPD OFF) and the ON stage (IPD ON)), for power on low (<1.5 Hz) and high frequencies (>1.5 Hz) at different moments: (a) 4 s before environment change (−4–0 s); (b) immediately after environment visual till 4 s later (0–4 s); c) after 4 s till 8 s later (4–8 s). Non-parametric Mann–Whitney exact test was used for intergroup comparison, and Wilcoxon paired *t*-test for intragroup comparison on different time moments as follows: (−4–0 s) vs. (0–4 s); (0–4 s) vs, (4–8 s); and (−4–0 s) vs. (4–8 s). .Significant *p*-values were shadowed.

	Mean±SD			Intergroup p-value			Intragroup p-value		
	C	IPD OFF	IPD ON	C vs IPD OFF	C vs IPD ON	IPD OFF vs IPD ON	C	IPD OFF	IPD ON
−4–0 s							**−4–0 s vs. 0–4 s**		
Mean low power (μ)	1.400 ± 1.487	2.442 ± 1.915	5.256 ± 7.883	0.019	0.036	0.389	0.465	<0.001	0.107
Mean high power (μ)	1.653 ± 2.216	3.271 ± 2.427	2.497 ± 2.744	0.002	0.096	0.073	0.002	0.003	0.064
Mean IF (Hz)	1.751 ± 0.143	1.775 ± 0.407	1.509 ± 0.397	0.945	0.089	0.001	0.113	0.934	0.454
0–4 s							**0–4 s vs. 4–8 s**		
Mean low power (μ)	1.388 ± 0.844	3.662 ± 2.756	4.713 ± 4.577	0.001	0.043	0.720	0.568	0.404	0.762
Mean high power (μ)	2.362 ± 1.731	4.687 ± 3.091	3.187 ± 2.953	0.003	0.537	0.007	0.441	0.375	0.035
Mean IF (Hz)	1.826 ± 0.204	1.763 ± 0.394	1.564 ± 0.372	0.864	0.043	0.064	0.134	0.048	0.121
4–8 s							**−4–0 vs. 4–8 s**		
Mean low power (μ)	1.320 ± 0.623	3.809 ± 2.718	4.185 ± 3.878	<0.001	0.014	0.978	0.182	<0.001	0.277
Mean high power (μ)	3.300 ± 3.754	4.127 ± 3.078	5.871 ± 8.723	0.128	0.202	0.421	<0.001	0.029	<0.001
Mean IF (Hz)	1.905 ± 0.226	1.635 ± 0.387	1.701 ± 0.303	0.017	0.030	0.679	0.023	0.030	0.055

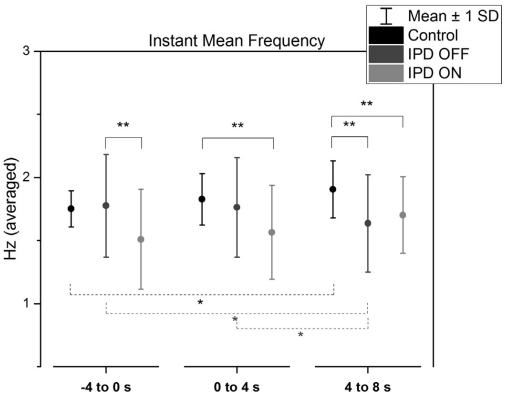

Fig. 3. Mean values of instantaneous mean frequency for healthy subjects (control) and IPD patients (in the OFF (IPD OFF) and ON (IPD ON) stages) averaged over 4 s intervals. Brackets with two asterisks represent statistically significant ($p < 0.05$) results of intergroup Mann–Whitney test. Brackets with one asterisk and dashed lines represent statistically significant ($p < 0.05$) results of intragroup Wilcoxon paired *t*-test.

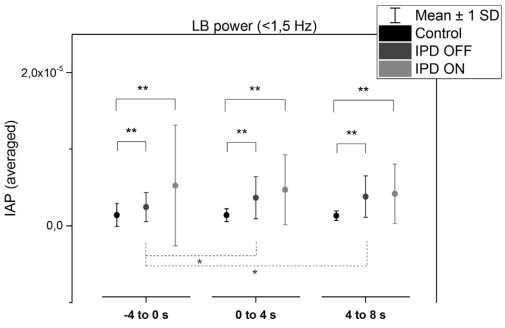

Fig. 4. Mean values of low frequency band power (<1.5 Hz) for healthy subjects (control) and IPD patients (in the OFF (IPD OFF) and ON (IPD ON) stages) averaged over 4 s intervals. Brackets with two asterisks represent statistically significant ($p < 0.05$) results of intergroup Mann–Whitney test. Brackets with one asterisk and dashed lines represent statistically significant ($p < 0.05$) results of intragroup Wilcoxon paired *t*-test.

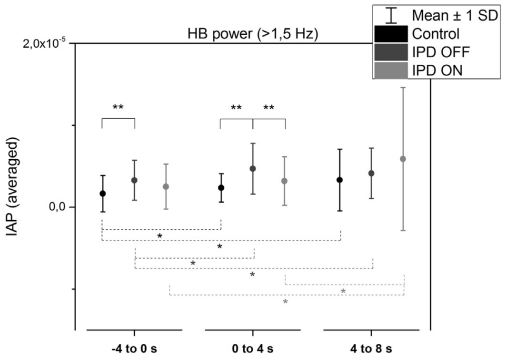

Fig. 5. Mean values of high frequency band power (>1.5 Hz) for healthy subjects (control) and IPD patients (in the OFF (IPD OFF) and ON (IPD ON) stages) averaged over 4 s intervals. Brackets with two asterisks represent statistically significant ($p < 0.05$) results of intergroup Mann–Whitney test. Brackets with one asterisk and dashed lines represent statistically significant ($p < 0.05$) results of intragroup Wilcoxon paired *t*-test.

(−4–0 s vs. 0–4 s ($z = -3.258$, $p < 0.001$); −4–0 s vs. 4–8 s ($z = -3.206$, $p < 0.001$)).

- High band (HB) power

IPD patients in the OFF state exhibited a significantly greater power than healthy subjects in the pre-stimulus condition (C vs. IPD OFF) (−4–0 s: $U = 56.0$; $z = -3.00$; $p = 0.002$). This observation remains true immediately after the perturbation (C vs. IPD OFF (0–4 s: $U = 59.0$; $z = -2.90$; $p = 0.003$)), which was also perceived in comparison between ON and OFF states (IPD OFF vs. IPD ON (0–4 s: $p = 0.007$)).

An abrupt increase of power took place in the first 4 s after the visual perturbation (−4–0 vs. 0–4 s): (control ($z = -2.94$; $p = 0.002$), IPD OFF ($z = -2.79$; $p = 0.003$), IPD ON ($z = -1.874$, $p = 0.064$)). Albeit IPD patients in the OFF state also had an increase of power (−4–0 s vs. 4–8 = s): ($z = -2.172$, $p = 0.029$), it was not as striking as in healthy subjects and IPD in the ON state, specialy at the 4–8 s interval (−4–0 vs. 4–8 s: control ($z = -3.260$, $p < 0.001$) IPD ON ($z = -3.408$, $p < 0.001$)). In fact, the constant increase of the HB power in IPD patients in the ON state is observed during the whole post-stimulus time interval (Fig. 5) (0–4 vs. 4–8 s: ($z = -2.101$, $p = 0.035$)).

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4. Discussion

IPD patients, besides a motor output disorder, have also sensory and perceptual impairments, rendering them more vulnerable to misjudgments of sensory feedback [48]. Postural control and other cognitive processing share cognitive resources, and performance of postural tasks is often impaired by a secondary cognitive task. Individuals who have limited cognitive processing due to neurological impairments, such as IPD, may use more of their available cognitive processing to control posture [49], increasing their susceptibility to falls. Moreover, there is growing scientific evidence that CPA in reaction to external perturbations are compromised in IPD [2,17]. Therefore, we hypothesized that a moving immersive virtual reality environment would be a useful tool for analyzing CPA in response to visual perturbations on healthy subjects in comparison to IPD patients, and further understand the role of levodopa and thereafter the underlying mechanisms of corrective postural adjustments.

Stiffer systems, as those representing subjects with IPD, are characterized by frequent and rapid adjustments of COM position [19,11]. Patients with IPD in the ON state increased their sway velocity, magnifying the difference comparatively to healthy subjects (Table 2). Our results are in agreement with this finding since IPD swayed at a faster velocity than healthy subjects. As shown in Fig. 2, prominent differences between groups occurred mainly in the vertical direction (Z-axis). CPA on the vertical axis probably reflects a human mechanism of maintaining balance by varying the height of COM through knees and trunk bending. In this respect, levodopa may have facilitated this postural control mechanism by reducing muscular stiffness and rigidity. However, as further discussed on study limitations, the clear instruction to maintain a quite stance and use knee-bending as a corrective strategy, may have potentially played a greater role in observing prominent differences in CPAs along the vertical axis. The role of levodopa in balance maintaining is not straightforward and investigations concerning postural instability in subjects with IPD that depend on quiet stance features, often produce discrepant results. Some research suggests that levodopa improves some balance abnormalities but worsens the others [50,51]. In the ON state, IPD patients may present larger and faster sway just because levodopa reduces rigidity without improving control of posture, or because subclinical dyskinesia increases body motion [19].

Higher velocities and displacements of postural adjustments may just reflect the mechanical consequence to control the COM. However, different central postural control mechanisms may be continuously and dynamically taking place and therefore TDF analysis may provide further information on the postural reaction and susceptibility to visual perturbation. Since, we did not find distinct peaks in distinct bands due to a particular event, we suggest that all frequency components have an active role in standing balance. However, control mechanisms can actuate on specific frequency bands by switching between stabilizing (low) and corrective (high) processes. In our study, TFD analysis of vertical acceleration revealed that compensatory postural adjustments, in response to visual perturbation, were taking place in two distinct bands: a low (<1.5 Hz) and a high frequency (>1.5 Hz) band. This meets the findings of other studies, which demonstrated that postural control takes place in two distinct time scales: a fast (high frequency) open-loop control and a slower (low frequency) corrective feedback-based control [1]. LB components seem to be largely dictated by the inertial properties of the oscillating mass of the subject. In contrast, HB oscillatory components of sway are more likely to represent the lump sum of irregular, voluntary and involuntary muscle activity and multisensory feedback integration [52]. Moreover, performance on cognitive tasks has been shown to be only influenced by the variability of fast sway components [35].

In our study, the dissonance of the visual input with the somatosensory perceptions (proprioceptive and vestibular), provoked by VR, induced CPA. These CPA were most evident immediately after visual environment scenario change but carried on till 8 s later. The immediate period after visual environment change may be the most important for major compensatory postural correction. After that other mechanisms, like reaction to minor details of the visual environment, may play their hand. These postural corrections seem to happen predominantly on the high-frequency spectra, as illustrated in Fig. 5. Immediately after the environment visual scenario change, IPD patients in the OFF state significantly reacted with higher power on HB than healthy subjects. However, IPD patients in the OFF state presented a different trend in comparison to Controls and IPD patients in the ON state. After the visual perturbation, IPD in the ON state had a similar trend to respond to visual perturbation in the HB similar to healthy subjects, which was even more prominent in the last interval.

As previously stated postural control that takes place in the HB probably reflects a more central cognitive and volitional mechanism of postural control [35,1], A recent study using VR and gait analysis on IPD, provided evidence that cognitive dysfunction, such as anxiety, interfered with proper information processing. On this study, dopaminergic medication improved utilization of sensory feedback in stressful situations by reducing anxiety and/or improving resource allocation [53]. Our findings (summarized in Table 3) corroborate the benefit of levodopa, as IPD in the OFF state presented more dependence of CPAs on the HB, further attenuated after levodopa in the ON state.

Healthy subjects maintained their LB frequencies power essentially unchanged, even after the visual perturbation. On the other hand, an abrupt increase of high frequencies power occurred after the stimulus onset. Lower frequencies probably reflect a more mechanical automatic oscillation mechanism of stabilization and posture control, dependent on the stiffness of the musculotendinous structure. Fig. 4 suggests that in the ON state, previous to visual perturbation, CPAs in the LB are more pronounced in comparison with the other groups. Probably, the inherent higher instability on IPD requires a greater actuation of continuous restoring and compensatory forces, which is provided by slow acceleration components. This strategy, achieved with levodopa treatment, is reflected by a significant shift of IMF towards the low frequencies in subjects with IPD in the ON state. These slow oscillations might indicate an improvement of muscle rigidity of IPD patients in the ON state. Without levodopa, IPD patients exhibited a need for a rapid increase of corrective adjustments on the HB, and afterwards a need for greater restoring effect provided by the LB. This probably reflects a higher susceptibility to the visual perturbation and need to produce corrective adjustments to external perturbations in the OFF state of IPD. Moreover, the trend to LB CPAs in the OFF state may indeed reflect the mechanical constraint of muscular rigidity. The passive stiffness of the musculotendinous structure of the human body stands out when maintaining quiet erect posture (as still as possible), either for the muscle completely relaxed or with muscle tone. The passive stiffness acts similar to an "elastic" opposed to the torque of gravitational force, which has the tendency to cause a forward fall of the body. Although the estimative of the contribution of the restoring torque due to the passive stiffness varies widely in the literature, it is estimated that this torque ranges about 65% to 90% from the magnitude of the gravitational torque [54,55] . Therefore, more than half of the torque responsible for maintaining our erect posture would be generated by a purely passive component, independent of the direct participation of the nervous system [56].

On previous literature, using a surface perturbation platform and electromyographic (EMG) analyzes of the automatic gastrocnemius or tibialis anterior muscle responses, it was shown that IPD patients had slower sensoriomotor responses and more difficulty in

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using cognitive set to modify their responses [15]. In this study levodopa medication did not improve the Parkinson subjects' ability to change set quickly [15]. In another study, with similar methodology, levodopa medication improved tonic background postural tone but further weakened automatic postural responses to external displacements [14]. On a multidirectional perturbations surface reactive forces and EMG trunk and limb analyzes, it was shown that IPD subjects, evaluated in OFF state, present excess activation of antagonist muscles across many perturbation directions. Their limited ability to modify postural muscle activity with changes in stance width, from wide to narrow stance, supported the hypothesis that the basal ganglia are important for optimizing muscle activation patterns by quickly switching motor patterns when the task or environment changes [17].

Locomotion and postural control involve cognitive volitional initiation and automatic controlled movement processes, such as the adjustment of postural muscle tone and rhythmic limb movements. Information processing between the basal ganglia, the cerebellum, and the brainstem may enable automatic regulation of muscle tone and rhythmic limb movements in the absence of conscious awareness. The basal ganglia play an important role in the control of axial tone, postural response amplitude, and interpretation of somatosensory information [57] . Thus, postural abnormalities in early IPD are not surprising. According to our results, this automatic postural control is responsive to levodopa and happens in a lower frequencies band. Intentional postural and gait modification, e.g., reacting to a visual obstacle and environment, requires motor programming in the premotor cortices. These motor programs utilize one's bodily information, such as the body schema, which is preserved and updated in the temporoparietal cortex. The motor programs are transmitted to the brainstem by the corticoreticulospinal system, so that one's posture is anticipatorily controlled [57]. According to our results, these volitional postural responses happen in a higher frequencies band.

5. Study limitations

Studies that have shown distinct timescale mechanisms for postural control, a low and a fast, have defined cut-offs of 0.3 Hz for COP position data [1,35]. Accelerometer data requires a new analysis in a range of frequencies from 0.3 to 3.5 Hz to determine which frequency would yield a proper discrimination between slow and fast components of postural sway. In our study, to distinguish between low- and high-frequency domains, a band separation at 1.5 Hz was chosen, as upon a visual inspection it appeared to yield representative and discriminative results. Nevertheless, this decision was purely subjective and should be explored further. Retrospective analysis of our clinical records revealed that 8 out of 15 IPD patients had at least one minor fall without injury, on the past two years. Our small sample impaired further robust statistical inference. As falls are very prevalent and important issue on IPD, further studies, with larger samples, are needed for kinematic analysis of CPAs to be used as an additional instrument to predict and differentiate different risks of falls. The clear instruction for subjects to maintain a fixed posture, with feet together position, and use knee-bending as a corrective strategy, may have potentially played a greater role in observing prominent differences in CPAs along the vertical axis (z-axis). Had they not been given these specific instructions upfront, the CPAs may have shown different patterns along different axes. As so, our methodology, albeit allowing better standardization between subjects and justifying our time frequency analyzes on the vertical axis (z-axis), has to be taken with caution as may not reflect the real life scenario, where a forward or lateral step correction, or use of lateral muscles, usually happen on freely open space. Furthermore, CPAs have shown to be higher in lateral muscles, especially on older, fallers and non-fallers, patients [5]. Nevertheless, using a narrow stance evaluation is very similar to the normal IPD progression, as patients with late-stage PD tend to stand and to walk with narrower and narrower stance width, and evaluating patients on narrow stance may further elicit differences to controls [58,17], as shown in our study.

6. Conclusion

In summary, our results showed that a VR model, which produced a sensorial dissonance between a changing visual environment in contrast to static sensorial inputs, induced significant compensatory postural adjustments on healthy subjects and IPD patients. Different postural adjustment mechanisms took place in LB and HB frequencies. LB aspects of CPAs are due to inertial properties of the oscillating mass, and, therefore, more dependent on the effect of levodopa on stiffness and rigidity. The HB oscillatory components of CPAs are more likely to represent multisensory feedback integration and a reaction to the ongoing visual input-changing scenario. IPD patients in the OFF state exhibited an abnormal compensatory response to the visual stimulus. Levodopa allowed these patients to perform with similarly to healthy subjects and lowered the HB response immediately after the visual perturbation. On the other hand, levodopa compensated the inherent instability of the IPD condition through an increased stabilizing force provided by low frequencies. This effect probably reflects a decrease of muscular stiffness and rigidity. Despite the overall larger and faster sway in the ON state, levodopa seems to improve CPAs in patients with IPD. Further studies are needed to evaluate CPA on VR paradigms with more open-space free movements, and even in real life scenarios.

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Chapter 3.5.

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Compensatory Postural Adjustments in an Oculus Virtual Reality Environment and the Risk of Falling in Alzheimer's Disease.

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Original Research Article

Compensatory Postural Adjustments in an Oculus Virtual Reality Environment and the Risk of Falling in Alzheimer's Disease

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Key Words
Alzheimer's disease · Falls · Compensatory postural adjustments · Oculus virtual reality · Time-frequency distribution · Inertia measurement units

Abstract
Background/Aims: Alzheimer's disease (AD) patients have an impaired ability to quickly reweight central sensory dependence in response to unexpected body perturbations. Herein, we aim to study provoked compensatory postural adjustments (CPAs) in a conflicting sensory paradigm with unpredictable visual displacements using virtual reality goggles. ***Methods:*** We used kinematic time-frequency analyses of two frequency bands: a low-frequency band (LB; 0.3–1.5 Hz; mechanical strategy) and a high-frequency band (HB; 1.5–3.5 Hz; cognitive strategy). We enrolled 19 healthy subjects (controls) and 21 AD patients, divided according to their previous history of falls. ***Results:*** The AD faller group presented higher-power LB CPAs, reflecting their worse inherent postural stability. The AD patients had a time lag in their HB CPA reaction. ***Conclusion:*** The slower reaction by CPA in AD may be a reflection of different cognitive resources including body schema self-perception, visual motion, depth perception, or a different state of fear and/or anxiety.

Introduction

Around 30% of people aged more than 65 years living in the community and more than 50% of those living in residential care facilities or nursing homes fall every year, and about half of those who fall do so repeatedly [1]. With the growing elderly population, the number

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of falls in this group has also increased [2]. Postural stability degrades with aging and is a factor for the occurrence of falls, especially in neurodegenerative diseases such as Alzheimer's disease (AD). These balance deficits are characterized by excessive and uncontrolled sway [3]. AD is the major cause of dementia in the geriatric population in the USA and Western Europe, but it is also associated with posture and gait disturbances [4, 5]. In fact, falls are more frequent and have more serious traumatic consequences, including hip fracture, in individuals with AD than in nondemented elderly people [6]. However, the underlying mechanisms contributing to falls in AD patients are still not clearly understood.

Anticipatory postural adjustments (APAs) and compensatory postural adjustments (CPAs) are the two main mechanisms used by the CNS in order to deal with body perturbations that may either be internally or externally generated [7]. When postural perturbation is unpredictable, postural muscles are activated to restore stability after the moment of perturbation. These later responses (CPAs) are triggered by sensory feedback signals and help in dealing with the actual effects of a perturbation [8, 9]. While APAs are observed only in the case of predictable perturbations, CPAs are seen during both predictable (following APAs) and unpredictable perturbations, which often are of a larger magnitude [10]. The absence or degradation of any type of sensory input or higher cortical control may affect balance performance, that is CPAs [11–13]. CPAs have shown to be greater in lateral muscles, especially in older faller and nonfaller patients [10].

The postural control mechanism is a spatially and temporally dynamic process dependent upon the external environment and system status [14–16]. Control characteristics may change over short periods of time, perhaps adapting to updates from sensory information [12]. Impaired sensory and motor systems increase the central processing load to maintain postural balance. The attentional resources may not be available due to cognitive impairments and central processing disorders. Patients with AD demonstrate a decline in postural control due to cortical deficits associated with impairments to sensory organization, such as suppression of visual or auditory distractions, dual-tasking, and diversion of attention to another focus [17–19].

Numerous studies have also reported that postural responses occur on two distinct timescales: a fast (high-frequency) open-loop control and a slower (low-frequency) corrective feedback-based control [19, 20]. Despite the lack of a clear distinction between slow and fast sway components, the lower frequencies can be attributed to the inertial properties of the oscillating mass and the high-frequency components are the net contribution of irregular voluntary and involuntary muscle activity, as well as the product of multisensory feedback integration [20]. In a previous study [21], we shed light on the dynamic control of posture, in particular CPAs, by using a time-frequency analysis of CPAs in a changing virtual reality (VR) setting in idiopathic Parkinson's disease (IPD) patients. CPAs were actuated in two different frequency bands: a low-frequency band (LB; 0.3–1.5 Hz), representing the mechanical properties of oscillation on postural correction, and a high-frequency band (HB; 1.5–3.5 Hz), reflective of the higher cognitive strategies of postural correction.

An appropriate nonstationary technique, such as time-frequency analysis, should be employed to characterize the existing dynamic variations [22]. The concept of time-frequency distributions (TFDs), as functions of both time and frequency, was introduced to circumvent the limitations intrinsic to stationary signal analyses [23]. One of the first solutions presented implements an extension to traditional Fourier analysis: the short-time Fourier transform. This estimates the energy spectrum (spectrogram) using a sliding window, thus assuming local stationarity of the signal. The resulting spectrogram depends on the window size, which is responsible for the trade-off between time and frequency resolutions. The bigger the window size, the better the frequency resolution and the ability to detect low-frequency components that are characteristic of postural adjustments. On the other hand, it sacrifices a

large amount of time information, which is especially critical when analyzing short-duration signals. This is the major limitation to spectrograms, making them unsuitable for center of mass (COM) data analysis [22, 24]. The minimum mean cross-entropy (MMCE) method combines information from a finite set of spectrograms computed with different window sizes, producing a much better approximation of the time-varying spectrum than any of these individual spectrograms. Investigations with the MMCE method have pointed out its low computational demand and ability to closely approximate positive TFDs of the Cohen-Posch class, which are the most appropriate for real-world signal analysis [25].

In the last years, the impact of visual perturbation on postural adjustments has been widely explored. In AD patients with a previous history of falls, postural control seems to be more vulnerable to the loss of visual input, increasing several postural sway parameters [26]. Susceptibility to visual stimulation has been studied in several conditions such as with a visual focus on differently distanced targets [27] or exposal to a moving surround, which in most of the recent studies was implemented through an immersive virtual scene allowing for a better perception of the induced motion. This VR creates an illusion that puts the subject in a place other than where he/she physically is [28]. Besides inducing the illusion of self-motion, the moving visual surround conflicts with perceptions from the somatosensory and vestibular systems, since the body does not actually move. As a consequence, the body generates CPAs in the direction of the visual perturbation [29, 30], which affects elderly and impaired subjects on a larger scale [12, 31].

Some studies pointed out the sensitivity of the vertical component to detect changes in postural balance [21, 32]. Settings comprising force platforms restrict their analyses to the 2D plane beneath the feet of the evaluated subject. If a vertical visual motion is evaluated, these data might not be able to properly reflect postural responses [29]. Inertial measurement units have emerged as tools complementary to conventional posturography, providing additional information about body tilt and orientation with the advantages of lower cost, reduced size, and portability [33, 34]. Given the prevalence of falls and the risks associated with them among patients with AD, the present study was designed in a way to submit participants to visual downward displacements mimicking the illusion of falling. Patients with AD perform poorly in tests of shifting visual attention or incongruent visual stimuli, suggesting a decreased ability to suppress the conflict induced by visual stimulation [17]. This finding motivated the design of an experiment where participants are immersed in a VR with unexpected visual displacements.

The primary objective of this research was to study postural adjustment mechanisms in AD, evaluating visually induced CPAs in a changing VR scenario in healthy subjects and AD patients by means of kinematic and time-frequency analyses on inertial measurement unit records. As a second objective, we aimed to relate the CPA profile to the risk of falling in AD by considering distinct groups of patients with AD (i.e. patients with and without a previous history of falls).

Methodology

Subjects and Clinical Assessment

The study protocol was approved by the local ethics committee, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants in the study. Twenty-one AD patients were consecutively recruited from our dementia outpatient consult who fulfilled the criteria for probable AD according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related

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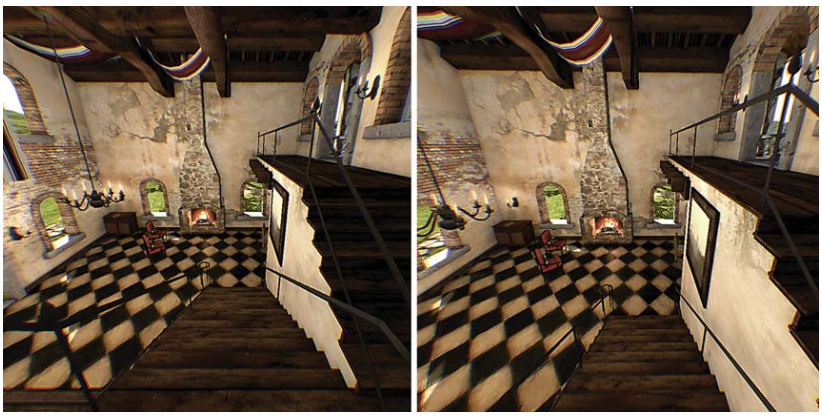

Fig. 1. Virtual environment created via Oculus Rift goggles, with the two translation scenarios: at the top of the staircase (left) and, after a visual displacement of 1.17 m along the vertical axis, translation to the middle of the stairs (right). Reproduced from Yelshyna et al. [21] (by permission of Darya Yelshyna).

Disorders Association (NINCDS/ADRDA) [35] (a score of 1 on the Clinical Dementia Rating scale). The control group consisted of the same 19 healthy subjects (controls) already used for a previous publication [21]. The exclusion criteria were orthopedic, musculoskeletal, and vestibular disorder, significant auditory deficit, and alcohol abuse and somatosensory deficit.

The recruited patients had normal vision dispensing with the use of glasses or contact lenses to correct their vision. Assessment of falls in the 12 months prior to assessment was carried out via fall calendars. A fall was defined as an unexpected event in which a participant comes to rest on the ground, the floor, or a lower level [36]. AD patients were recorded as fallers (AD fallers) if they had had at least one fall in the previous 12 months, in contrast to nonfallers (AD nonfallers). The collected variables consisted of demographic (gender, age, and education) and anthropometric data (weight, height, and body mass index). Clinical data were also collected – including years of disease duration and a neuropsychological examination using the Portuguese version of the Montreal Cognitive Assessment (MoCA) with scores normalized to the Portuguese population [37] – no more than 1 month prior to the kinematic assessment. Levels of education were categorized by years of schooling as follows: 0 (analphabetic), 1 (1–4 years), 2 (5–9 years), 3 (10–12 years), and 4 (>12 years).

Apparatus and Postural Tasks

For this study, we implemented the same methodology as previously reported in the study on Parkinson's disease [21]. One sensing module, harboring an 8051 microprocessor embedded in a CC2530 Texas Instrument SoC (system on chip), and a wearable inertial measurement unit (MPU6000; triaxial accelerometer and gyroscope), operating with a sample rate frequency of 118 Hz on an SD card [38], were attached to the COM, located at 55% of the patient's height above the ground.

The subjects were submitted to a realistic visual scene with 3D depth information by wearing Oculus Rift goggles – a VR headset device with a 100-degree field of view. Visual focus and eye width settings were adjusted for each participant to display a clear stereoscopic 3D image. Tuscany Demo (fig. 1) was the chosen scenario for subject evaluation. Several objects

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were embedded in the virtual scene: floor, roof, stairs, fireplace, chandelier, window, and door. In this virtual environment, the subjects stood at the top of the staircase, with the purpose of performing unexpected, visually induced motions and evaluation of the response to the illusory perception of falling (translation down the stairs). While performing the tasks, the subjects were instructed to keep standing still, barefoot, with the medial aspects of their feet touching each other, with their arms hanging at their sides and using a safety trunk belt. The subjects were instructed not to abandon this position and, if need be, to make a corrective adjustment by bending their knees.

Each participant underwent a preparatory phase. They were asked to identify and search for several objects embedded in the VR setting so that they could feel fully immersed in the environment. Inside the virtual environment, the subjects stood at the top of the staircase and were issued to focus their attention on the first stair below their feet. Approximately 10 s later, the scenario instantaneously moved down, creating a visual displacement, translating the subject to the middle of the stairs. After another 10 s, the scenario moved upwards, placing the subject back on the top of the stairs, until the next trial. After experiencing several translations, the subjects were asked to state if they felt that they were virtually pushed onto the middle of the stairs, as they would have experienced in real life. This procedure was repeated several times, with a minimum of a 20-second gap between trials and a minimum of 5 preparatory trials per subject, so as to guarantee immersion in the VR setting, as assessed by the subjects' answers about having the feeling of subjective immersion in VR. Previous studies, also focusing on perturbations, have shown that our intertrial time intervals were adequate, as the participants were able to change sets from one condition to another [39].

With the same methodology as for the preparatory phase, a total of 5 effective downward trials per subject (10 s duration) were selected as the object of subsequent analysis. The neurologist was responsible for triggering the downward translation in a manual and random fashion, thus averting adaptation and a learning effect and keeping individuals unaware of the exact moment of the upcoming event. The visual perturbation in VR elicited no need for a corrective step in either group. The translation in the virtual environment corresponded to approximately 1.17 m of displacement along the vertical axis.

Data Analysis

No clear procedures have yet been established for accelerometer data processing, but the main energy content of human movement is held below 3.5 Hz [33, 40]. For this reason, the raw acceleration signals were filtered with a zero-phase low-pass Butterworth filter with a 3.5-Hz cutoff frequency. Due to the abdominal placement of the sensor, acceleration signals went through additional high-pass filtering in order to eliminate interference that might be caused by the act of breathing. Considering a normal respiratory frequency in adults (i.e. 18 breaths/min [41]), we applied a zero-phase high-pass Butterworth filter with a 0.3 Hz cutoff frequency. A more precise evaluation of visual destabilization is achieved when the subject is focused and unaware of the upcoming event. Tasks that require precise eye fixation, as in a visual search for objects in the surrounding environment, appear to decrease sway variability [42]. In order to identify this increased attentional demand during quiet stance, we computed the TFD's total power in the HB (1.5–3.5 Hz) 4 s prior to the visual stimulus for all trials and selected the one with the lowest value. This trial was considered most representative of the response to visual stimulation and was evaluated by means of kinematic and time-frequency analyses.

Kinematic Analysis

Descriptive statistics such as standard deviation, maximum, minimum, and range were computed for the acceleration signals for the three axes, as well as for the orientation and

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displacement estimates. Also, the common features related to COM excursion (e.g. sway area and sway path) were computed from the estimated COM position [11]. Kinematic measures were computed from 8-second time segments immediately after the onset of the selected visual downward-moving stimulus.

Another version of the accelerometer signal – one that takes lower frequency components into account – was considered in order to characterize body orientation and to approximate its displacement [26, 34]. For this purpose, both the raw acceleration and gyroscope signals underwent zero-phase low-pass Butterworth filtering with 0.5- and 2-Hz cutoff frequencies, respectively. A detailed explanation of the methodology used to obtain body orientation – pitch and roll angles – and an estimate of COM displacement and acceleration can be found in our previous study [26].

Time-Frequency Analysis

In a previous study [21], we shed light on the dynamic control of posture, in particular CPAs, by using a time-frequency analysis of CPAs in a changing VR setting with IPD patients. CPAs were actuated in two different frequency bands: LB (0.3–1.5 Hz), representing the mechanical properties of oscillation on postural correction, and HB (1.5–3.5 Hz), reflective of higher cognitive strategies of postural correction.

For each subject, we extracted time segments including all trials with a margin of 10 s prior to the first and after the last stimulus. The time-varying spectrum was estimated by an MMCE combination Hann window of spectrograms computed with windows of 15, 31, and 127 samples [25]. Using this large time segment including all the trials performed, it is possible to obtain a TFD with a high time and frequency resolution. Afterwards, the relevant trial was identified, and only the corresponding portion of the TFD 4 s before and 8 s after stimulus onset was extracted to perform further computations (fig. 2). The Time-Frequency Toolbox (v1.2) for MATLAB© provided the function for MMCE computation.

A quantitative description of dynamic TFD behavior can be achieved by defining several time-dependent parameters, including instantaneous average power [43, 44]. The instantaneous average power allows monitoring sudden changes due to postural adjustments. This feature was computed for each of the frequency bands considered (HB and LB) for 3 time intervals: the 4-second interval prior to stimulus onset (–4 to 0 s) and two 4-second intervals after stimulus onset (0–4 s and 4–8 s). All data processing and feature computation were performed with a custom-made MATLAB© code.

Statistical Analysis

Gender comparisons were analyzed by the χ^2 Fisher exact test. Given the small number of subjects, the intergroup statistical analysis was carried out with a nonparametric Kruskal-Wallis test, with a pairwise post hoc analysis with Dunn's test. The computations were performed with a Monte Carlo simulation with a 99% confidence level. The Wilcoxon matched-pair test was used for assessing the intragroup magnitude of changes for the separate band powers of TFD analysis. Statistical analyses were conducted with the software SPSS v.20.0.

Results

Subjects

Twenty patients with AD (11 fallers, 9 nonfallers) and 19 controls were included in this study. The demographic and anthropometric characteristics of the three groups are summarized in table 1. The groups were equally matched according to demographic and anthropometric characteristics. AD patients, as expected, presented with lower scores on the MoCA

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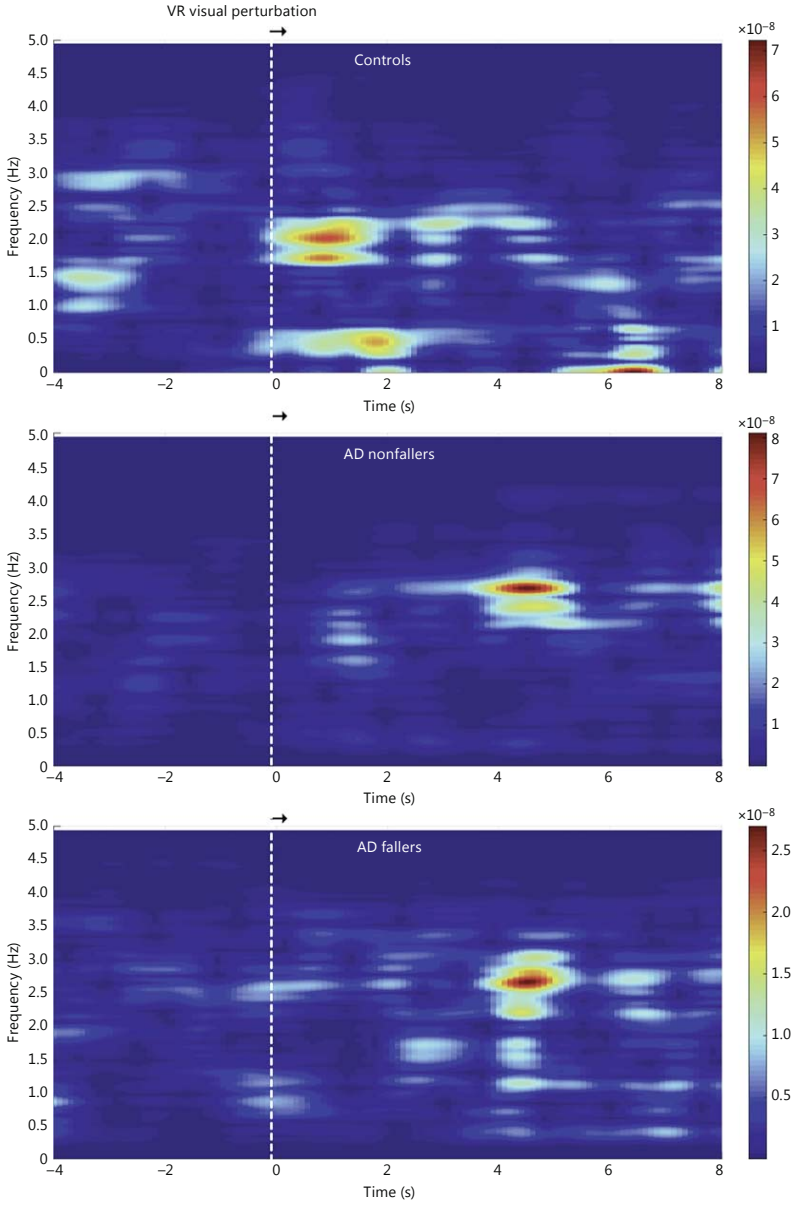

Fig. 2. Examples of TFDs obtained from the representative trial for each of the groups studied: controls, AD fallers, and AD nonfallers. The visual downward perturbation occurred at 0 s.

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Table 1. Demographic and clinical data on controls, AD fallers, and AD nonfallers

	Controls (n = 19)	AD fallers (n = 11)	AD nonfallers (n = 9)
Gender (female/male), n	11/8	9/2	5/4
Age, years	71 (51–78)	76 (66–82)	75 (61–82)
Weight, kg	75 (56–107)	66 (42–80)	66 (54–86)
Height, m	1.63 (1.49–1.79)	1.51 (1.41–1.77)	1.58 (1.44–1.69)
Body mass index	28 (22.9–33.4)	26 (18.8–34.8)	27 (21.9–39.7)
Level of education	1 (0, 2)	1 (0, 2)	1 (0, 1)
MoCA score*	24 (18–30)	9 (5–19)	12 (7–17)
Disease duration, years	–	3 (2–4)	3 (3–5)

Data are presented as medians (min.–max.). For levels of education, see Methodology. * Statistically significant difference on Kruskal-Wallis intergroup comparison.

($p < 0.01$; controls vs. AD fallers: $p < 0.001$; controls vs. AD nonfallers: $p < 0.001$). However, there was no statistical difference in MoCA score or disease duration between the two AD groups.

Kinematic Features

The vertical acceleration signal demonstrated a greater power in discriminating AD fallers from controls. The AD faller group presented a higher range of acceleration on the z-axis (controls vs. AD fallers: $U = 38.0$, $z = -2.862$, $p = 0.003$), with a higher mean acceleration ($U = 53.0$, $z = -2.216$, $p = 0.026$), root mean square acceleration ($U = 57.0$, $z = -2.044$, $p = 0.042$), and average acceleration magnitude ($U = 53.0$, $z = -2.216$, $p = 0.026$) (fig. 3).

Time-Frequency Distributions

The TFD analysis reflected pronounced differences in the frequency patterns of CPAs in response to visual perturbation, perceived at the separate power band levels in the various time intervals before and after visual perturbation. The control, AD faller, and AD nonfaller groups perceived and reacted to visual perturbations with different patterns (table 2).

In comparison to the controls, the AD nonfaller group had significantly higher values of power of CPAs only in the HB, and only just before visual perturbation (–4 0 s). In contrast, the AD faller group had significantly higher values of power of CPAs both in the LB (<1.5 Hz) and the HB (>1.5 Hz) during all time intervals (fig. 4, 5), i.e. before (–4 0 s) and immediately after visual perturbation (0–4 s) as well as at the end (4–8 s).

In the intragroup analysis of the pattern of progression of CPAs in the different time intervals, none of the groups had significant changes in power in the LB. In the HB, only the control group had a significant increase in power immediately after visual perturbation (–4 to 0 vs. 0–4 s), a reaction also present towards the end (0–4 vs. 4–8 s). In contrast, the AD faller and nonfaller groups had a delayed reaction, with a significant increase only in the last interval (0–4 vs. 4–8 s).

Discussion

Different central postural control mechanisms may be continuously and dynamically taking place, and therefore TFD analysis may provide further information on the postural reaction and susceptibility to visual perturbation. Some studies have demonstrated that

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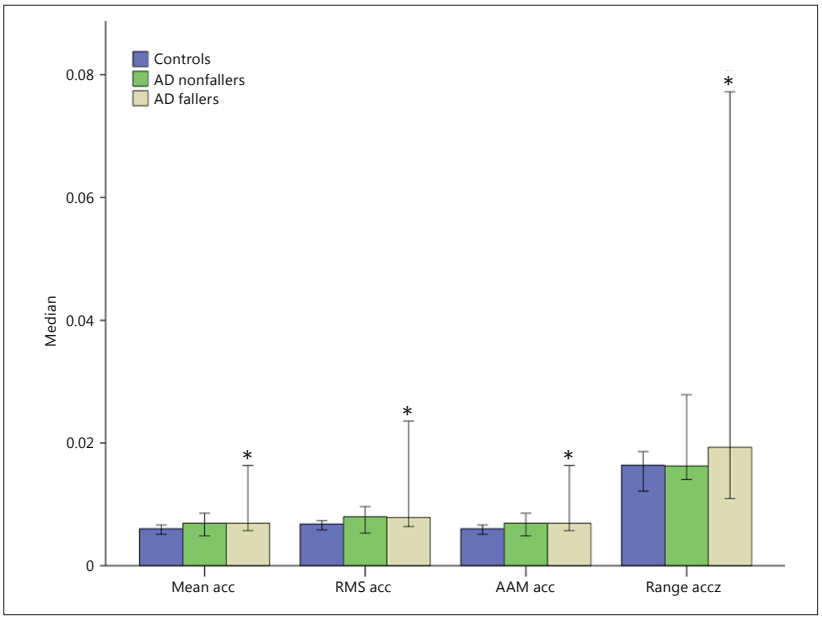

Fig. 3. Errors bars (95% confidence intervals) of the median values of the acceleration measures mean acceleration (acc), root mean square (RMS) acceleration, average acceleration magnitude (AAM), and range of acceleration on the z-axis (Range accz) for healthy subjects (controls), AD fallers, and AD nonfallers. The AD faller group had statistically significantly (* $p < 0.05$) higher values versus the control group.

postural control takes place on two distinct time scales: a fast (high-frequency) open-loop control and a slower (low-frequency) corrective feedback-based control [21, 45]. Indeed, LB components seem to be largely dictated by the inertial properties of the oscillating mass of the subject, reflecting a more mechanical automatic oscillation mechanism of stabilization and posture control that is dependent on the stiffness of the musculotendinous structure. In contrast, HB oscillatory components of sway are more likely to represent the lump sum of irregular voluntary and involuntary muscle activity and multisensory feedback integration [46]. Moreover, performance on cognitive tasks has been shown to be only influenced by variability in the fast sway components [20]. In our study, the dissonance between visual input and somatosensory perceptions (proprioceptive and vestibular) provoked by VR induced CPAs. These CPAs were most evident immediately after the visual environmental scenario change but carried on for 8 s (fig. 4, 5). In this study, using the same methodology as in our previous study [21], we showed that AD fallers clearly presented CPAs with higher values of acceleration and with a different pattern of distribution of power in the LB and HB.

CPAs in the LB

Our VR paradigm, with a translation within the virtual environment of 1.17 m along the vertical axis, did not elicit any significant destabilization that required CPAs in the LB in any of the groups. Nevertheless, AD fallers had more pronounced CPAs in the LB irrespective of

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Table 2. Instantaneous average power in the LB (<1.5 Hz) and HB (>1.5 Hz)

Power	Controls	AD nonfallers	AD fallers	Intergroup p value			Intragroup p value		
				C vs. AD fallers	C vs. AD nonfallers	AD fallers vs. AD nonfallers	C	AD fallers	AD nonfallers
–4 to 0 s							–4 to 0 vs. 0–4 s		
LB, μ	49,269 ± 153,186	75,092 ± 54,267	107,734 ± 213,439	*0.021*	0.156	0.552	0.992	0.638	0.426
HB, μ	38,452 ± 227,522	90,412 ± 102,705	137,576 ± 113,418	*0.001*	*0.037*	0.131	*0.002*	0.067	0.074
0–4 s							0–4 vs. 4–8 s		
LB, μ	53,887 ± 55,417	93,178 ± 100,454	86,086 ± 561,911	*0.018*	0.188	0.456	0.352	0.067	0.426
HB, μ	87,021 ± 170,807	141,058 ± 112,508	200,029 ± 1996,252	*0.012*	0.117	0.331	*0.01*	*0.005*	*0.020*
4–8 s							–4 to 0 vs. 4–8 s		
LB, μ	58,180 ± 40,505	74,877 ± 96,107	123,381 ± 396,144	*0.008*	0.383	0.261	0.953	0.557	1.000
HB, μ	102,373 ± 371,794	125,411 ± 191,455	286,321 ± 659,403	*0.011*	0.156	0.175	0.490	0.206	0.496

Data are presented as medians ± standard deviation unless specified otherwise. Significant p values are in italics. Descriptive table of instantaneous average power (median ± 1 standard deviation) in the LB (<1.5 Hz) and HB (>1.5 Hz) on the z-axis during different time intervals: 4 s before environment change (–4 to 0 s), immediately after visual perturbation till 4 s later (0–4 s), and from 4 s till 8 s later (4–8 s). Pairwise post hoc analysis of intergroup comparison [controls (C), AD fallers, and AD nonfallers] and Wilcoxon paired t test analysis of intragroup comparison.

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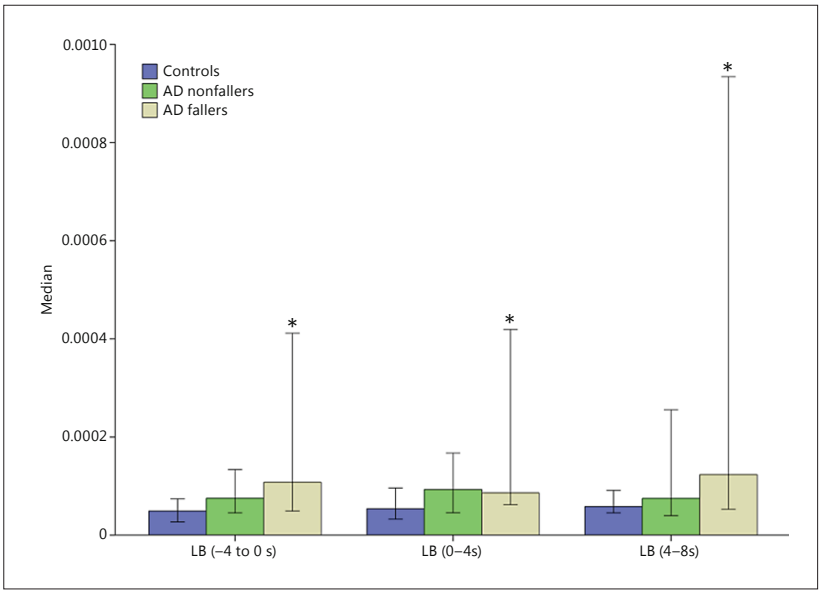

Fig. 4. Errors bars (95% confidence intervals) of the median values of the power in the LB (<1.5 Hz) for healthy subjects (controls) and AD patients (fallers and nonfallers), averaged over 4-second intervals (–4 to 0, 0–4, and 4–8 s). There was a statistically significant difference (* $p < 0.05$) on Mann-Whitney intergroup comparison between controls and AD fallers. There were no statistically significant changes between the different intervals in any group.

the different time interval and response to visual perturbation. As already stated, the LB reflects a subconscious automatic oscillation mechanism of stabilization and posture control that is dependent on the stiffness of the musculotendinous structure. Thus, our findings may reflect an inherently higher instability of AD faller patients, requiring greater actuation of continuous restoring and compensatory forces, provided by the slow acceleration components.

CPAs in the HB

With due limitations to any extrapolation to real-life scenarios, our moving, immersive VR environment was a useful tool for analyzing CPAs in response to visual perturbations and to further comprehend the underlying mechanisms of corrective postural adjustment. In our VR environment, several cognitive, emotional, and sensorial conflicts occurred simultaneously. After visual perturbation, all subjects required corrective adjustments in the HB, thus corroborating the role of higher cognitive processes in postural control.

We found that healthy subjects had an immediate response to the visual perturbation and an inherent increase in CPAs in the HB. In contrast, the AD faller and nonfaller groups had a delayed reaction, with a significant increase only during the last interval, after 4 s. Also, besides responding with a time lag in reaction to the visual perturbation, AD fallers had higher CPAs in the HB. This clearly reflects their higher vulnerability to visual perturbation and the

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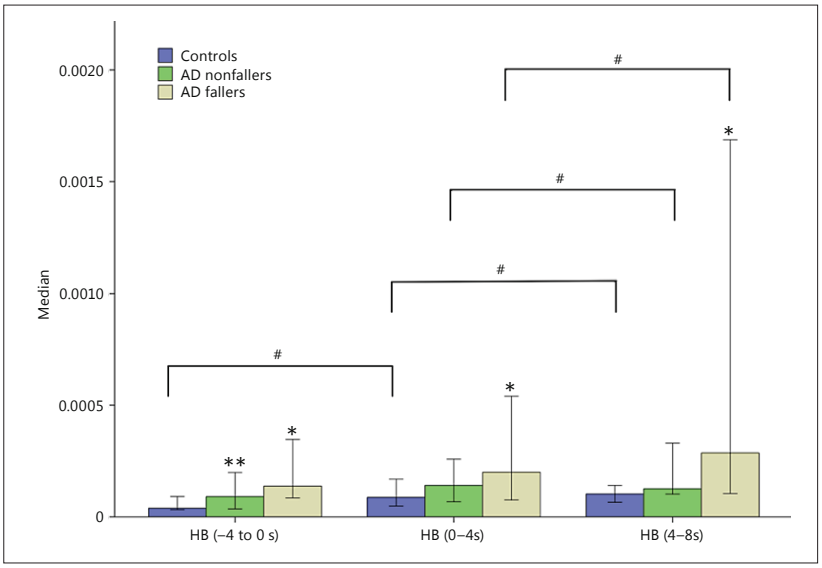

Fig. 5. Errors bars (95% confidence intervals) of the median values of the power in the HB (>1.5 Hz) for healthy subjects (controls) and AD patients (fallers and nonfallers) averaged over 4-second intervals (–4 to 0, 0–4, and 4–8 s). There was a statistically significant difference on Mann-Whitney intergroup comparison between controls and AD fallers (* $p < 0.05$), and between controls and AD nonfallers (** $p < 0.05$). Brackets with a hash mark ($^{\#}$ $p < 0.05$) represent significance on intragroup Wilcoxon paired t tests. The control group had a statistically significant increase during the first interval (–4 to 0 s). All groups had a statistically significant increase between the second (0–4 s) and the last interval (4–8 s).

need to produce corrective adjustments to external perturbations in order to maintain the COM within the limits of stability [17–19].

Several hypotheses can be raised to explain this profile of delayed and higher CPAs to external perturbations in AD fallers. Postural control that takes place in the HB probably reflects a more central cognitive and volitional mechanism of postural control [20, 45]. With aging, the attentional demands of postural control increase as sensory information decreases, and the inability to allocate sufficient attention to postural control under multitasking conditions may be a factor contributing to imbalance and falls in some older adults [3]. Patients with AD demonstrate a decline in postural control due to cortical deficits associated with impairments to sensory organization, such as suppression of visual or auditory distraction, dual-tasking, and diversion of attention to another focus [17–19]. Response inhibition, an executive cognitive function, allows one to ignore irrelevant sensory inputs, overcome primary reflexes, filter out distractions, respond discriminatively to important features in the environment, and focus on postural stability [47]. The impaired ability of the CNS to quickly reweight sensory dependence in AD (even when the peripheral sensory system is intact) in response to dynamic perturbations in the sensorial environment during daily life increases the risk of falling [17]. Individuals who have limited cognitive processing due to neurological impairments, such as AD patients, may need to use more of their available cognitive processing

to control posture [48], increasing their susceptibility to falls. In fact, the slower reaction time to postural perturbations in AD has been associated with a higher risk of falls [49, 50], corroborating our results.

AD nonfallers and fallers – even if they may appear similar on initial clinical and demographic evaluation – may have different cognitive resources available for postural control and, ultimately, a higher risk of falling. In comparison to healthy subjects, our visual scenario of imminent and unpredictable falls could have elicited higher COM imbalances in AD patients, demanding higher CPAs in the HB. A recent study using VR and gait analysis in IPD patients provided evidence that cognitive dysfunction, such as anxiety, interfered with proper information processing [51]. The reaction to an unexpected visual perturbation, such as in our VR paradigm, required that body schema self-perception and motor programming be preserved and adequately updated in the temporoparietal cortex. The finding of delayed and more exacerbated CPAs in the HB in the AD faller group may be a consequence of a more severe atrophy of the temporoparietal cortex. In the absence of brain imaging in our study, this hypothesis deserves further exploration. Interestingly, some studies have reported that the hippocampus uses vestibular information for spatial memory and navigation, and that balance impairment could be related to reduced hippocampal performance [52]. Another point of view is that the delayed reaction of our AD patients when facing the visual-vestibulosomatosensory conflict posed by the VR paradigm could also be due to impairments of visual motion, shape [53], and depth perception [54] reported in AD. Furthermore, threat-related factors influence the neuromechanical postural responses to an unpredictable perturbation, and these responses may be facilitated in younger healthy adults [55]. Thus, the emotional state, such fear of and anxiety about falling, may explain different CPA responses among AD patients, in particular in AD fallers.

Study Limitations

Our small sample impairs robust statistical inference, and thus our results have to be taken with caution. Our exclusion criteria – in particular the absence of visual, musculoskeletal, vestibular, and auditory deficits – clearly contributed to the smallness of our sample. These deficits are extremely prevalent in geriatric populations and, if not excluded, would have been an even greater confounder for the interpretation of CPAs. Studies that showed distinct timescale mechanisms for postural control, a low and a fast one, defined cutoffs of 0.3 Hz for center-of-pressure position data [20, 45]. Postural analysis with accelerometer data requires an assessment in the range of frequencies from 0.3 to 3.5 Hz to determine which frequency would yield a proper discrimination between slow and fast components of CPAs. In this study, to distinguish between low- and high-frequency domains of CPAs, a band separation at 1.5 Hz was chosen, since upon visual inspection it appeared to yield representative and discriminative results, using the same methodology as in our previous work [21]. Nevertheless, this decision was purely subjective and should be explored further. The clear instruction to the subjects to maintain a fixed posture, with their feet together, and to use knee-bending as a corrective strategy may have potentially played a greater role in the prominent differences in CPAs along the vertical axis (z-axis) observed [21]. This is important, because in a real-life scenario, forward or lateral step correction, or the use of the lateral muscles, usually happens in free open space. Moreover, CPAs have been shown to be greater in the lateral muscles, especially in older faller and nonfaller patients [10]. As already mentioned, executive functions have an important role in CPAs, and decreased executive functions are associated with worse performance on functional measures of balance [56]. This could be further explored in a broader neuropsychological examination in a future study.

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Conclusion

The impaired ability of the CNS to quickly reweight sensory dependence in AD (even when the peripheral sensory system is intact) in response to dynamic perturbations in the sensorial environment during daily life increases the risk of falling. Our VR paradigm, which produced a sensorial dissonance between a changing visual environment and static sensorial inputs, induced significant CPAs in healthy subjects and AD patients, especially in the HB. Different postural adjustment mechanisms were at work in the LB and HB. The postural adjustment mechanisms in the LB reflect the inertial mechanical properties of the oscillating mass of the body, whereas in the HB, they represent higher cognitive multisensory feedback integration and reaction to the ongoing scenario of changing visual inputs. Our AD fallers presented a higher power of CPAs in the LB, reflecting an inherently higher instability of AD fallers and the requirement of continuous restoring and compensatory forces, provided by the slow acceleration components. The AD patients presented delayed CPAs in the HB, with a significant time lag to visual perturbation in comparison to the healthy subjects, with the AD fallers needing greater CPAs. This delayed profile of CPAs to visual perturbations and misjudgments of sensory feedback may be a reflection of slower reaction times due to different cognitive resources and/or errors, including body schema self-perception in the temporo-parietal cortex, visual motion and depth perception impairments, or a direct consequence of different emotional states such as fear and anxiety and a higher risk of falling.

Analyses of postural adjustment kinematics in different VR settings and paradigms, translating the more complex real-life challenges into a standardized and controlled mode, may allow better comprehension of the different (mechanical, sensorial, and higher cognitive) systems that play a role in postural control. As falls are very prevalent and an important issue in AD, further studies are needed, with larger samples, to prove that kinematic analysis of CPAs is a useful tool for clinical practice in identifying patients with higher risks of falling and, therefore, allowing the implementation of preventive measures.

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CHAPTER 4 – DISCUSSION

Human postural control and locomotion abilities develop over several years, from childhood to adult age, in different age milestones[66]. Athletes can develop special skills of equilibrium and, in contrast, patients (e.g. vestibular lesions; musculoskeletal deficits) are able to compensate with the remaining systems[43].The owns body's perception in relation to space, the body schema, that develops and adapts through during our entire life, resides in cortical structures [45]. It is thus not surprising that with aging and even more in neurological diseases, where there is cortical involvement, postural control is less effective and the risk of falls is higher[6]. Still, in different neurological diseases with cortical involvement, such as AD and IPD, it is not certain to what extent and how differently neuropathology affects postural control networks (cortical and subcortical), albeit clinically presenting with the apparently same postural instability. As a counterpoint, there is growing evidence that different diseases, along their neuropathological progression, have overlapping network dysfunctions and thus overlapping clinical spectrum[67]. For example, extrapyramidal dysfunction, where increased tonus (rigidity) is a paramount clinical feature of IPD, may be also present in AD[26].These doubts, justified our investigation, where quantitative and objective analysis provided by postural control analysis may surpass medical observational limitations, allow differentiating diseases in different stages of disease. Notwithstanding, some fundamental questions have also to be tackled alongside clinical studies. Postural control is based on corrective torque generated from active feedback-control mechanisms based on body motion detected from different sensory systems[47]. However, the postural control model, in specific the integration of all the feedback-control mechanisms from these systems, is still unknown. Using paradigms where each system can be isolated and manipulated (e.g. eyes closed), can provide some insight on how the remaining system behave. In our research, different paradigms (eyes open, eyes closed, background noise suppression, inclined platform, incongruent visual-somatosensory inputs under VR) proved to be an adequate experimental apparatus to study the dynamic reweighting and multisensorial integration of postural control. Also, these paradigms proved to be sufficient to differentiate AD patients from healthy subjects [68-70], IPD patients from healthy subjects[71], and IPD from VPD patients[72].

In the following sub-chapters, we revisit our findings and elaborate a discussion where the current knowledge of postural control (in particular neural networks, neurobiology, neurophysiology and conceptual postural control models) is integrated with potential implications in neurodegenerative diseases, and put forward open questions to be tackled in future research.

4.1. Multisensorial integration in postural control

In order to maintain postural equilibrium, sense movement and have a proper awareness of the relative location of our body parts in relation to surrounding space, the human body integrates information coming from several body's sensory and response systems including visual, vestibular, somatosensory (touch, pressure, and stretch receptors in our skin, muscles, and joints), and auditory systems. Combining and integrating multisensorial inputs reduces redundancy and increases reliability of gait and postural control [45]. The merge of all these sensory information results in a perception of one's body and is conceptually defined as "body schema" [46]. The temporoparietal-posterior parietal cortex seems to be the likeliest common ground structure where the body schema is generated [73]. The premotor and supplementary motor areas use this body schema to generate the motor programs that are critical for locomotion, postural control with postural adjustments[20]. In our research, the change of postural sway upon disturbance in the visual, auditory and somatosensory system and after levodopa medication, is the basic proof that postural control dynamically integrates information coming from different systems, compensating and reweighting different systems, in order to maintain the COM within the limits of stability.

In the following paragraphs, we discuss our findings, sustaining the evidence that postural control is a product of multisensorial integration and how this may improve our knowledge of neurodegenerative diseases.

Visual system

We have shown that visual suppression had a negative impact on postural stability, in healthy subjects but also in patients with IPD, VPD[72] and AD[74,75]. This is in line with other studies, which have also found increased postural sway in mild cognitive impairment and AD patients upon visual suppression[14]. Within AD patients, AD with higher incidence of falls (AD faller), presented higher vulnerability to visual suppression[74]. AD fallers, besides swaying more (total displacement), swayed beyond safety limits (maximal displacement). In AD[74], we have shown that mediolateral sway was associated with a higher risk of falls, and that the anteroposterior sway is a discriminative parameter of AD. Our results are in agreement with previous literature, which also found increased postural sway in mild cognitive impairment and AD patients upon visual suppression[14], but also that mediolateral sway is associated with a higher risk of falls in elderly people[76]. Also, anteroposterior sway has shown to be a discriminative parameter of AD versus controls[14] and fallers versus non fallers in cognitively able older people[77].

Auditory system

We have confirmed that audition plays an important role in the multisensory integration of postural control in healthy subjects [69]. To the best of our knowledge, there were no previous work investigating the role of the auditory system in postural control in AD. We have shown that

background noise suppression reduced postural sway in healthy subjects and AD patients[69], in line with other works where silencing or using an auditory white noise, in healthy young adults and adults over the age of 65 years, with and without vision input, was shown to reduce postural sway[78]. When subjects are placed in an environment where background noise does not provide any meaningful spatial location cues, suppressing this noise, with ear defenders [69] or music (instrumental music without lyrics [1]), has a positive effect on postural stability.

In order for the auditory signals to be translated into a meaningful sound, such as language, it is required central processing within the primary auditory cortex and other higher order cortical association areas. It is very likely that the auditory systems and postural control share the same resources with higher cognitive functions. Thus, patients with neurodegenerative diseases, may have higher vulnerability to unpredictable auditory challenges. Further research, making use of auditory stimulus, predictable/unpredictable, dual-task paradigms, may further enlighten this topic.

Rehabilitation sensory therapies, involving tactile and auditory stimulus, are being explored to reduce increased balance variability due to typical age-related sensory declines[27,79]. Auditory feedback, whether alerting when limits of stability are overpassed and the risk of falling is high, either by eliciting a more subconscious state of postural control, through active noise cancellation headphones (reducing low frequencies (e.g. traffic sound), but still allowing high frequency (e.g. voice)), may be a future tool for prevention of falls.

Cognition and emotion

In our work, we have shown that CPA, happening in the high frequency band, are a mirror of higher cognitive, volitional feedback loops [70,71]. There is considerable research showing that postural control and higher cognitive processing share cognitive resources (e.g. prefrontal circuitry), and performance of postural tasks is often impaired by a interfering cognitive task [80]. It is thus not surprising, that dual task paradigms[31], or increasing difficult postural control tasks[74,75], often illicit more differences in postural control performance between patients and healthy subjects. In fact, dual and multitask challenges are the most frequent situation in real life, where individuals have to tune volitional cognitive tasks (e.g. talking) with multisensorial information (e.g. visual and sound information), that often are unexpected or even dissonant [70,71]. The inability to allocate sufficient attention to postural control under multitasking conditions may be a factor contributing to imbalance and falls in some older adults[81]. Under our VR sensorial conflicting experiment, both AD and IPD patients (OFF state), needed higher CPA in the HBA, reflecting higher demand of cognitive resources. Also, AD fallers had a time lag in theirs CPAs in the HB. This is in concordant with previous findings, associating slower reaction times to postural perturbations to a higher risk of falls in AD[62]. Our results are also consistent with previous findings, where AD patients perform poorly in tests of shifting visual attention or incongruent visual stimuli, suggesting a decreased ability to suppress the conflict induced by visual stimulation[65]. Indeed, higher susceptibility to sensorial disturbance,

manifested by increased susceptibility to sensorial disturbance, may be a reflection of higher risk to fall in AD [68,70].

IPD patients in the OFF state, significantly reacted with higher power on HB than healthy subjects[71]. Conversely, in the ON state, IPD behaved similar to healthy subjects. It is thus evident, that under restrictions of COM adjustment (OFF state), cognitive resources of postural control are over activated in IPD. This resource allocation can be counterproductive, as frequently executive cognitive functions are impaired in IPD[82]. Our findings are in line with a previous VR study where dopaminergic medication improved the use of sensory feedback in stressful situations by reducing anxiety and/or improving resource allocation[54]. In contrast, others have shown that levodopa does not improve CPA as well as it improves voluntary adjustments [83]. This research suggests that other brain regions, outside of the basal ganglia, such as areas related to ACh, contribute more to reactive postural control strategies, and be less impacted by levodopa therapy [83].

Human movement is also dependent on emotional status[20]. Threat-related factors influence postural responses to an unpredictable perturbation[84]. Projections from the limbic hypothalamus to the brainstem, result in emotional motor behaviours such as fight-or-flight reactions[20]. Thus, the emotional state, such fear of and anxiety about falling, may have consisted in underling factors explaining the different CPA responses of AD patients, in particular in the AD fallers group [70]. In another study, also using VR and gait analysis, it was provided evidence that emotional dysfunction, such as anxiety, interfered with proper information processing in IPD[54]. In the HB, regardless of being healthy subject or patient, all subjects had a significant increase of their power after visual perturbation [70,71], proving the volitional mechanism of postural control [85,86].

4.2. Neurophysiology and conceptual models of postural control

A better knowledge of the neurophysiology and conceptual modelling of the human postural control where the weight of each system per si can be isolated is paramount to better comprehend the network underlying cortical integration, and further advance in the comprehension of postural instability in neurodegenerative diseases.

Postural control happens within feedback and feedforward CNS loops (cortical, subcortical and spinal networks) integrated with the peripheral system. Each of these systems, networks and loops has its own intrinsic electrophysiological properties and/or velocity of processing [66,82]. However, there is scarce information on how and if all these information and electrical activity can be translated to a conceptual postural control model, where the weight of each system is quantified into a mathematical equation. Some simulation experiments have proposed a feedback model-based model where postural control results from a dynamic reweighting of sensory contributions, rather than a load-compensation mechanism with fixed combination of

sensory-orientation information[47]. Clearly, this a field in need of extensive research. In the following paragraphs, we display findings of our research, where the issue of neurophysiology and the conceptual model of postural control were approached.

There is much evidence that there is a transient increase in body sway after restoration or alteration of visual-orientation cues[47]. This is particularly evident in elderly subjects, due to a reduced ability to rapidly reconfigure the postural set[47]. Indeed, postural control happens with a relatively time delay of 150–200 ms [47]. This delay maybe the necessary time to properly integrate and reweight the influence of all systems, avoiding uncontrolled gain feedback responses if each system acted by its own. In our work, we used a time window of 30 seconds with feet in the ground or in an inclined platform[72,74], manipulating visual and/or auditory information[75]. This methodology has the merit of reflecting the sum average of postural adaptation in response to sensorial deprivation, ultimately allowing a conceptual extrapolation of each system weight on postural control. Yet, considering the delay of sensorial integration of 150–200 ms, a time window of 4 seconds, as in our VR dissociative visual-somatosensory paradigm[70,71], maybe more adequate if the research is focused on the velocity of CPA, that have been showed to be delayed in elderly subjects and even more in neurodegenerative diseases[47,70].

In our research the absence of vision had a negative impact on postural sway varying from 15% to 30% in healthy subjects and AD patients, respectively[75]. Although, eyes closing is a very useful paradigm, it barely grasps the complexity of the visual systems such as motion, depth and visual gnosis perception. It is important to acquaint, especially in our VR paradigm, that visual detection of motion decreases linearly with an increase of the angular velocity of the moving object from 1 to about 50 degrees/sec[87]. Even more complex is visual depth and gnosis perception, which are dependent on the visual cortex and other higher order cognitive functions, which may also be impaired in AD and IPD[16]. These aspects are beyond the scope of this thesis but, in future research, especially when using VR paradigms, visual processing and perception has to be taken into account.

Vestibular information is important to maintain an internal, updated representation of the body position and movement in space, being paramount at velocities above 2 degrees/second of body sway[43]. In contrast, the somatosensory system acts at lower velocities (below 2 degrees/second), being sufficient to control postural sway without vestibular information [43]. The mechanical properties of the musculoskeletal system, such as its passive torch, start to exert its influence (e.g. ankle dorsiflexion to align the upper bodies with respect to a moving surface instead of to gravity) only on faster movements (above 8 degrees/second of postural sway). However, even though the muscle stretch-reflex feedback is very fast (a relatively short time delay 25-ms transmission delay plus an additional delay with similar magnitude due to muscle activation and force development) it makes a limited contribution to postural control in contrast to other systems[47]. In daily life, the postural control system makes very limited use of

graviceptive cues in conditions where other sensory systems provide redundant orientation information. Still, in a moving surface, subjects discount the proprioceptive information and shift toward increased reliance on graviceptive information [47]. Taking this in account, in our work, even on the inclined platform, having the subjects the time to adapt, we essentially analyzed an average of postural control corrections, and a reweighting and shift from visual to proprioceptive information (without the influence of graviceptive inputs)[74].

There is mounting evidence that postural responses occur on distinct timescales, as a reflection of different delays and electrical activity in the different networks [66,82]. Some studies have demonstrated that postural control takes place on two distinct time scales: a fast (high-frequency) open-loop control and a slower (low-frequency) corrective feedback-based control [67]. The lower frequencies can be attributed to the inertial properties of the oscillating mass (dependent on the stiffness of the musculotendinous structure) and the high-frequency components are the net contribution of irregular voluntary and involuntary muscle activity, as well as the product of multisensory feedback integration [66]. In our work[71], we have confirmed this hypothesis and shown that CPA enclose different mechanisms acting on different time scales: a low frequency band (LB)(<1.5Hz) (representing a mechanical oscillating mass strategy); and a frequency band(HB) (>1.5 Hz), representing a cognitive postural mechanism).

Time frequency analysis of postural sway, used in our research[70,71], has been previously used to conceptualize on different postural control models[47]. Time frequency analysis of postural sway is based on the premise that each system has its own intrinsic neurophysiological channel, with intrinsic velocity noise and neural controller, that ultimately can be captured on the frequency of postural sway. On a previous experiment, it was proposed that postural control operates close to a stability limit between 0.1- or 1-Hz body sway[47]. Enhanced low-frequency (~0.1 Hz) body sway indicates an under-generation of corrective torque, whereas enhanced high-frequency (~1 Hz) sway indicates an over-generation of torque[47]. These limits are below our proposed 1.5hz cut-off, but in contrast in our study we took in consideration the impact of cognitive mechanisms.

4.3. Implications for Neurodegenerative diseases

In this chapter, we converge our previous discussion over multisensorial integration, neurophysiology and conceptual models, with current knowledge over neurobiology of the different neural networks involved in postural control, to elaborate on the implications of our results in neurodegenerative diseases, raising further questions and future lines of research.

Implications in IPD

The diagnosis of clinically established IPD, even though the importance of ancillary tests has been raising, is essentially centered on clinical criteria[88]. Definitive diagnosis is based on neuropathology and includes evidence of alpha-synuclein deposition and death of dopaminergic

cells within the substantia nigra pars compacta [88]. As so, dopamine is the main disturbed neurotransmitter in IPD. However, even in very early stages of IPD, there is also evidence of alpha-synuclein deposition in other structures, such as the pedunculopontine nucleus (PPN) and nucleus basalis of Meynert (nbM), that release acetylcholine (ACh), and the locus coeruleus, that releases noradrenaline [89]. Even the cerebellum, where the inhibitory neurotransmitter GABA plays a central role, is also altered in IPD[90].

In IPD, levodopa improves bradykinesia and rigidity, which explains the observed improvement in some domains of gait (e.g., reduced step length, gait velocity, pace, arm swing, etc.)[22]. In contrast, other domains, such as gait timing and postural sway, are unaffected or even worsened, respectively, by levodopa[22]. As such, the influence of dopamine in postural control remains still very controversial. Moreover, from early to advanced phases of IDP, current clinical evidence is mostly centered in the correction of levodopa deficits. Without doubt, acetylcholinesterase inhibitors are only prescribed when cognitive impairment is present, most of the times in more advanced stages of IPD[88]. In a recent clinical trial, IPD patients with previous history of falls but without dementia were assigned to a double-blind, placebo-controlled, rivastigmine, to the target dose of 12 mg per day, over 12 weeks[91]. It was found that rivastigmine can improve gait stability and might reduce the frequency of falls. It thus deserves further investigation, if starting acetylcholinesterase inhibitors in earlier phases of IPD, even without previous history of falls, can have a beneficial impact in IPD. Interestingly, falls in IPD, a prominent outcome of postural instability, have been correlated to cholinergic innervation from the PPN to the thalamus, with no similar loss in nigro-striatal dopaminergic denervation[92]. In fact, ACh in the thalamus (provided primarily by the PPN) has been correlated with falls in PD, whereas dopaminergic function has not[92]. In addition, medication that improves ACh availability (donepezil and rivastigmine) may reduce falls in people with PD[93]. However, as already mentioned, ACh also plays an important role in the nucleus basalis of Meynert cortical networks and volitional control of movement and postural responses. Thus, it is questionable if the observed benefit of ACh in reduced falls and gait stability[91,93], was due to improved attention and executive functioning or instead due to enhanced subcortical automatic responses of postural control. These issues demand further clinical trials with cholinesterase inhibitors.

In our VR paradigm of CPAs, we found that most of the benefit of levodopa in IPD was due to its effect in rigidity (muscle stiffness), diminishing the constraints for CPAs[71,72]. IPD patients, without the benefit of levodopa, had to reallocate cognitive resources for postural control[71]. This finding is extremely important, as a more conscious control of typically overlearned tasks is detrimental, by reducing postural performance and increasing the variability of gait and postural control[34]. In comparison to healthy subjects, IPD patients are more dependent on focused attention and external cues during gait and postural control [94], exhibiting larger than normal cortical activity, both when the task is new and after over- learning has occurred. This suggests a

higher shift to volitional control in IPD[35]. Indeed, it has been shown that IPD patients have decreased activity in the supplement motor areas (preferentially related to internally driven movement), and over activation of volitional networks such as the cerebellum and other cortical areas, like the premotor cortex[95]. Despite the slowed rates of adaptation and learning present in IPD, eventually patients can adapt gait and stepping patterns with repetition[96,97]. Therefore, VR can be a safe clinical environment, where patients can benefit from adaptation and repetition, reducing their fear and anxiety, thus setting a more subconscious automatic postural control state.

Implications in VPD

A significant controversy remains over the use of the term "Vascular parkinsonism" as an umbrella for any patient showing extra-pyramidal signs associated with abnormal white matter signal on neuroimaging[39]. Many cases reported as VPD may represent pseudovascular parkinsonism (e.g., Parkinson's disease or another neurodegenerative parkinsonism such as supranuclear palsy with nonspecific neuroimaging signal abnormalities), vascular pseudoparkinsonism (e.g., akinetic mutism resulting from bilateral mesial frontal strokes or apathetic depression from bilateral striatal lacunar strokes), or pseudovascular pseudoparkinsonism (e.g., higher-level gait disorders, including normal- pressure hydrocephalus with transependimal exudate) [39].

With this controversy in mind we purposely opted to include only the akynetic-rigid subtype of IPD, to be clinically matched as possible to VPD patients[72], that fulfilled previous published criteria for VPD[37]. Even if the clinical diagnosis of VPD is not consensual, we have shown that these VPD patients have a different postural stability profile[72]. VPD patients have higher anterior-postural postural sway, correlated with their gait disturbance burden, and also not responsive to levodopa. Therefore, the larger anterior-posterior range of postural sway may represent a distinctive variable of VPD[72] in comparison to IPD, where trunk sway and variability are more excessive in the mediolateral direction[64]. Similarly, also in AD[74], the most discriminative variable was postural sway in the anteroposterior axis. This may represent in AD and VPD, a lower threshold to postural instability of the anteroposterior ankle strategy, in contrast to the mediolateral hip strategy.

In our work, VPD patients had a very low improvement after levodopa challenge (medium of 19%), much lower than the 30% recommended in most recent MDS criteria for IPD[88]. In MDS criteria, it is recommended that patients with Parkinson's Syndrome should be challenged with a sufficiently high dose of levodopa daily (≥600 mg/d) to make a verdict of absence of response to levodopa. Nevertheless, it is questionable if, after IPD has been excluded and other atypical Parkinson's Syndrome like VPD is more likely, higher doses of levodopa should be aimed. Even though, the assumption that less rigidity is always better may come intuitively, at least from a pure biomechanical model standpoint, some doubts still persist. Postural lateral sway may be increased after taking levodopa, possibly due to reduced rigidity, but without improvement in

postural control [98]. As so, the central core of these doubts is essentially related to what is the most adequate dose. There are no clear guidelines on how much levodopa should be given, neither in IPD even less in VPD or other Parkinson's syndromes. On a clinical ground, rigidity is measured by clinical subjective impression on neurological examination, and the optimal dose of levodopa means reducing rigidity without causing dyskinesia. In lack of other technological alternative to mechanically analyze rigidity, postural analysis may be an additional tool for the clinician to objectively quantify the benefit of levodopa in rigidity and consequent effect on postural sway. In other words, postural analysis would allow to determine the maximum dose of levodopa after which there is no added benefit, for example by detecting subtle dyskinesia that are translated in faster postural sways.

In our research, in intermediate stages of IPD, patients without clinical postural instability (Hoehn-Yahr ≤2), postural control was still modulated by levodopa[72]. In contrast, in VPD, also without overt clinical postural instability, levodopa had no effect on postural sway, even less on the AP axis. It seems that the main benefit of levodopa was restrained to muscle tone in IPD, and other non-dopaminergic networks are possibly involved in VPD. Our findings in VPD and IPD support the evidence for the interconnection between locomotor and postural control networks, that are mainly non-dopaminergic [72,99]. VPD patients presented with higher mPIGD score mostly due to gait impairment. Our findings are in line with previous work, where it has been shown that locomotion and postural control (muscle tone control) converge and share several regions and networks[20]. Cholinergic PPN neurons activate the muscle-tone inhibitory system (pontine reticular formation neurons, inhibitory reticulospinal neurons descending from the dorsomedial ventromedial medullary reticular formation, and inhibitory interneurons in the spinal cord), regulating not only the level of postural muscle tone, but also rhythm and pattern of locomotion[20]. In contrast, nonoaminergic descending pathways (coerulo- and raphespinal tracts), and the reticulospinal tract from the ventromedial medullary reticular formation, belong to the muscle-tone excitatory system, but also activates the spinal rhythm- generating system. Also, GABAergic basal ganglia output from the internal segment of the globus pallidus (GPi) and the SNr to the mesencephalic lomotor region/PPN controls locomotion and muscle tone[20]. This is important, as excessive GABAergic inhibitory effects upon the MLR/PPN may be a pathophysiological basis of gait disturbance and muscle tone rigidity (hypertonus) in IPD[100]. With the above evidence in animals models in context combined with our findings[72], we can further speculate that in VPD, where increased muscle tonus was not responsive to levodopa, probably the main culprit is not an excessive inhibitory effect coming from the basal ganglia (as observed in IPD), but instead a dysfunction in the muscle-tone inhibitory system or an over activation of the muscle-tone excitatory system secondary to strategic and/or cumulative cerebrovascular lesion. Functional and Diffusion-tensor MRI imaging with fiber tractography, some already using VR paradigms[101], have been successfully used to study locomotor networks and can further confirm these hypotheses.

Although levodopa is very effective in reducing limb rigidity in IPD[72], it does not reduce axial rigidity as effectively [23,72]. This may be due to the fact that axial and limb rigidity are influenced by distinct pathways from dorsolateral (axial) and ventromedial (limbs) descending spinal systems[20]. This further reinforces the concept that other neurotransmitters, besides dopamine, are involved in postural control. As such, in VPD, non-dopaminergic networks, such as the PPN or MLR or even descending spinal pathways, may be affected by vascular pathology, and therefore not be responsive to dopamine.

Implications in AD

In our work we have shown that AD patients have increased reliance on visual inputs over other senses [75]. Even the positive effect of background noise suppression (-9% to -11% decrease in postural sway), was not sufficient to overcome the negative effect of visual suppression. This overreliance on visual system, is clearly negative and may explain the higher vulnerability to falls in AD[14], especially under reduced light environments, as it happens at night. In our research using a VR paradigm to study CPA in AD[70], we observed an overactivation of the higher cognitive modalities of postural control in AD, shown by the higher CPA in the HB of postural control. This shift towards a more volitional postural control, although meant to compensate for dysfunction of subcortical automatic pathways and/or different systems involved in postural control, it increases variability of gait and postural control and instability [35]. As so, this higher cognitive compensatory mechanism is detrimental. Indeed, the overdependence on conscious control, puts the patients more dependent on focused attention and external cues, and thus more vulnerable to the surrounding environment and risk of falling. Our work leads us to speculate that AD patients have less resources and more difficulty to adapt and compensate in response to daily life postural challenges. This supports the potential benefit of rehabilitation interventions, where response inhibition and filtering out and/or ignoring irrelevant and distracting auditory sensory inputs, may enable reallocation of resources toward focusing on better postural stability, set into a more autonomous and subconscious state[78]. We have also observed, that AD fallers had a time lag in theirs CPAs in the HB, which is in concordant with previous findings, associating slower reaction times to postural perturbations to a higher risk of falls in AD[62]. Furthermore, the hippocampus uses vestibular information for spatial memory and navigation, and it has been hypothesized that balance impairment in AD could be related to reduced hippocampal performance[102]. A delayed profile of CPAs to visual-vestibulosomatosensory perturbations may be a reflection of slower reaction times due to different cognitive resources and/or errors, including body schema self-perception impairments[103]. We can than speculate that AD faller group may have an increased atrophy of hipoccampus and/or temporoparietal cortex. Future investigation using volumetric MRI and postural analyses can further elucidate if slower postural reactions are due to cortical atrophy.

There is substantial evidence concerning the benefits of exercise on cognition, for instance increasing the production of brain derived neurotrophic factor, ameliorating insulin sensitivity,

reducing stress, and inflammation[104]. Tai Chi is a superb yet low impact balance and coordination exercise, that has been extensively applied with success in IPD and AD[105,106]. We can thus hypothesize that exercise, a continuous demand for postural control, exerts its benefit by stimulation of both unconscious and volitional modalities of postural control. Patients with higher cognitive reserve, due to education and occupational attainment, can compensate their deficits and be more resilient to structural pathological brain changes[107]. As so, the same principle can apply to exercise and postural control. Future prospective studies in healthy subjects should verify if exercise focused on postural control can, in the long run, reduce the risk of falling or even delay dementia.

Concerning the mechanical modalities of postural control, we found that in AD patients[70], especially fallers, had higher CPA in the LB. This is a clear reflection of the higher postural instability, and thus greater need for CPA in the LB with variation of muscle tone, in AD with falls. Even though extra-pyramidal signs are not the core clinical feature in AD, there is growing evidence that some AD patients develop extra-pyramidal signs, and its presence correlates to greater cognitive and neuropsychiatric impairment, probably due to neuropathological features typical of Lewy bodies disease[26]. Moreover, besides these overlapping neuropathological features, there is mounting evidence that different neurodegenerative diseases may also overlap in clinical and pathological phenotypes due to the disintegration of common neuronal networks[67]. Despite this, dopamine deficiency is clearly not the main feature of AD. Nevertheless, animal models could be a methodological approach in order to get a better insight of the degree of involvement of the extra-pyramidal system (dopaminergic and non-dopaminergic) in AD, especially in patients with higher risk of falls.

There are very few studies, with conflicting results, examining the effect of anti-dementia drugs (i.e., acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists) on postural control and gait in AD. Some have found no benefit of anti-dementia drugs[108], in contrast others have found that memantine may improve gait variability while single tasking, whereas acetylcholinesterase inhibitors may improve gait variability while dual tasking [109]. Different outcomes and methodological approaches may explain these conflicting results, and larger cohorts of patients, coming from multicenter labs, with a standardized assessment approach, are needed. At this stage, it is important to highlight the paradox of acetylcholinesterase inhibitors having different effects in the postural control, in IPD versus AD. In IPD, in contrast to AD[108], rivastigmine (acetylcholinesterase inhibitor) has mostly shown to have beneficial effects on postural control and gait[91,93]. We can put forward a neuropathological explanation for these differences. In IPD most of the neuropathology takes place in subcortical structures, where ACh is widely present in the PPN, whereas in AD neuropathology essentially involves cortical areas. Yet, we could at least expect a positive effect of the acetylcholinesterase inhibitors on executive functions, as ACh is also widely present in striatum and frontal circuitry involving the nbM.

Although AD and IPD share increased risk of falls due to postural instability, maybe different gait and postural control circuits are involved and/or in different stages of the disease. In fact, according to Braak stages, there is only involvement of cortical areas in more advanced stages of IPD, which is coincidental in the increased risk of falling in later Hoehn-Yahr stages of IPD [89]. Other point to acquaint is to separate studies using acetylcholinesterase inhibitors versus butyrylcholinesterase inhibitors [110]. Head-to-head studies, comparing gait and postural control studies both in IPD and AD, may provide further clues. In this respect, as CPA involves cognition, postural perturbations under dual-task paradigms, may be a useful tool in future studies.

4.4. New technologies in postural control analysis

New technologies have the potential to significantly improve both clinical diagnosis and management in neurological diseases, being an additional tool in the conduct of clinical studies. However, there are several challenges ahead, such as clinical validation of hardware devices[51], standardization of the methodologies of acquisition, and better understanding of the large-scale, high-dimensional character of the data captured by these wearable sensors into a meaningful information [111]. Machine learning algorithms have been used to tackle this issue of big data. Machine-learning algorithms make high-accuracy predictions and discover structure and relationships in complex data that would be well beyond the reach of any unaided human analyst to intuit[111]. Although hundreds of kinematic parameters have been used to represent postural body sway[112], it is still yet undertermined which parameters provide the most relevant information about postural control. With this question in mind, in parallel to the main focus of this thesis, we applied different machine learning classifiers to the data that we acquired in our AD patients and healthy subjects, namely Multiple Layer Perceptrons[113], Radial Basis Function Neural Networks, Support Vector Machines and Deep Belief Networks[114]. We observed that there is high inter-correlation between different kinematic postural variables[114], specially when data was normalized and adjusted for biometric characteristics, highlighting the difficulties in hand. Still, our machine learning algorithms delivered high rates of accuracy in the diagnosis, confirming its viability as a complementary tool in the forward investigation.

The application of wearable devices in AD has been slow when compared to the effort being made in IPD. Probably, the slower application of new technologies in AD may be due to the difficulty of designing safety protocols in cognitive impaired patients. In this respect, VR is a new technology that allows to mimic ecological paradigms (e.g. crossing a road), in safer and lab controlled environments, that in real life would be simply impossible or require complex facilities and numerous staff.

CHAPTER 5 – CONCLUSION AND FUTURE DIRECTIONS

In our research, we have proved that wearable devices are a valid complementary tool in the clinical analysis of postural control. Even though some pitfalls have to be recognized, for example standardization of measures, quantitative and objective analysis of postural control unravels new windows of research in clinical and neurophysiological domains.

From a neurophysiological point of view, many doubts still remain about postural control in humans. It is common knowledge that postural control is a corrective torque generated from the active feedback-control mechanisms based on the body motion detected from different sensory systems(somatosensory, vestibular, visual, auditory systems)[47]. Still, we lack information of the intrinsic electrical properties (e.g. velocity of processing) of these networks and how they integrate. In our work, different paradigms (eyes open, eyes closed, background noise suppression, inclined platform, incongruent visual-somatosensory inputs under VR), isolating and manipulating inputs, proved to be an adequate experimental apparatus to study the dynamic reweighting and multisensorial integration of postural control. Furthermore, enclosed in the raw signal of postural sway (using time frequency analysis), we were able to identify different frequencies reflecting different corrective feedback loop mechanisms[71]. In particular, a high-frequency loop, representing cognitive postural mechanisms, and a low frequency loop, representing mechanical oscillating mass mechanisms. This proves that different networks, with intrinsic electrical activity, are at play during postural control and are interconnected in feedforward and feedback loops. We have also shown that postural control is extremely dependent on vision, for self-orientation in space and for the generation of postural adjustments. In response to visual disturbance, there is a dynamic reweighting and reliance on the remaining systems, in particular increasing the gain of somatosensory inputs and/or auditory spatial clues. This was uniformly present in healthy subjects and in patients. Still, we were able to differentiate AD patients from healthy subjects [68-70], fallers from non-fallers, IPD patients from healthy subjects[71], and IPD from VPD patients[72].Even though the field of wearable devices in gait and postural control is still in its infancy, needing parametrization and cut-offs, our research is in line of its potential for differential diagnosis purposes.

Cognition has a major role in postural control, not only through attention and executive cognitive networks, but also as a reflection of the individual's expectations, awareness of “body schema” state, and prior experience (e.g. fear of falling)[84]. In our work, we have shown that in AD there is a delay in cortical processing of information, unleashing a self-feeding perpetual spiral of erroneous mechanical and cognitive adjustments, especially in AD with increased risk of falls[70]. Also, in IPD, we have shown that, even though levodopa may facilitate postural adjustments by reducing rigidity and body constraints, IPD patients impose a detrimental strain on cognitive resources[71]. This is in line with previous research that has shown that, although

the primary culprit of postural instability in IPD may rely in the cortico-basal ganglia-thalamocortical loop, which causes excessive muscle tone and hypokinetic postural adjustments, cognitive networks are also at play.

VR is increasingly used in many medical fields, consisting a safe tool for investigational and rehabilitation purposes. VR also allows to create incongruent states of reality and predictable/unpredictable dual-task paradigms. In our work, we have integrated two technologies, wearable devices with VR, taking advantage of VR to recreate an incongruent somatosensory-visual environment, with unexpected stimulus[70,71]. The VR paradigm, served the purpose of having a better insight of the multisensory integration of postural control. Most importantly, it served to show that cognitive resources are at play during postural control adjustments, and that patients with AD and IPD use these resources to compensate for their inherent postural instability. This is consistent with previous findings[35], indicating that there is an increased activation of the cerebellum and cortex in IPD which, despite compensating for impaired activity in other brain regions, results in a detrimental overdependence on external cues and a shift from an automatic to a more voluntary postural control.

Future directions

Studying postural control in static conditions has its own advantages, mainly when conceptualizing about the different postural control mechanisms and/or for differential diagnosis purposes[55]. Yet, the dynamic postural control during initialization and maintenance of gait and the postural adjustments (CPA and APA) to external perturbations during gait are a better reflection of what mostly happens in daily life. As such, studying dynamic postural control during gait is clearly a further step in our research. Gait analysis positions itself as an additional too in future areas of research, namely the role of multiple domains of cognition and emotion in postural control. Fear, one of the multiple cognitive domains, in particular the fear of falling, leads to activity restriction and detrimental spiral loss in the different systems involved postural control[84]. Considering that stressful events can shift the human behaviour from a healthy to a stressed pattern[115], with repercussion at a neurobiology and neural network level, it would be interesting to understand how this also happens in postural control domains.

Without doubt, the research in gait and postural control, at neurophysiological and clinical field domains, will continue to benefit from the integration of multiple tools (e.g. wearable devices; VR; EEG; brain MRI, etc.). As these technologies evolve, further effort is needed to envision new paradigms (e.g. conflicting vision and auditory context; intrusion noise vs. meaningful sound), where the manipulation of senses enlightens the different networks at play, and how they are differently impaired in neurodegenerative diseases. Also, further research is needed to better understand how cognitive and/or physical rehabilitation therapy can modulate responses to external cues/stimuli (e.g. eliminating a wrong postural response pattern to an external challenge such as obstacle crossing) and/or facilitate the shifting from a voluntary to a more automatic postural control (with less demanding on higher cognitive resources). In this respect,

VR may be an additional tool to pave the research in difficult areas, such as is fear, eliciting the recreation of complex cognitive paradigms. Also, our research of postural responses to auditory suppression in AD[75], unique to the best of our knowledge, has to be reproduced and evolve to study postural responses to predictable/unpredictable external auditory stimuli. Auditory feedback, alerting subjects when limits of stability are being overpassed and the risk of falling is high, would be a future tool for rehabilitation and prevention of falls.

The exploration of different drugs enhancing performance of gait and postural control and even cognition is another promising research field. Indeed, there is mounting evidence indicating that IPD may benefit from a dual therapeutic approach, dopamine plus acetylcholine enhancing drugs[91]. Even though it is pragmatic to think that each disease has one neuropathological starting point (in the case of IPD the pars compacta of the substantia nigra, that way affecting predominantly dopaminergic networks), it is also self-evident that in the CNS, networks are highly interdependently connected with non-restricted neurotransmitters (e.g. GABA, serotonin, noradrenaline, etc.). This goes in line with previous findings where different diseases, along their neuropathological progression, have overlapping network dysfunctions and thus overlapping clinical spectrum[67]. As such, we may question if in AD, where extrapyramidal dysfunction and muscle rigidity is also present [26], patients could also benefit from dopamine enhancing drugs. Furthermore, as cognitive resources are so important during normal gait and/or are used to compensate for deficits in subcortical networks, it is comprehensible that stimulant drugs, such as methylphenidate[116], have gathered so much attraction in recent years. Yet, if fear and erratic/exuberant postural responses to internal and external stimuli are also important, we can also question if we should use drugs that reduce excitability, such as GABA agonists/ergenic drugs. There are several challenges ahead for future clinical trials, particularly considering the hypothesis that a multiple drug strategy may outweigh the common single neurotransmitter symptomatic drug approach.

In our work, we have started with the initial premise that different neurodegenerative diseases (AD, IPD and VPD), albeit displaying an apparently similar higher vulnerability to external perturbations, under an umbrella term of “postural instability”, have impairments in different networks[67]. However, we have to acknowledge that different neurological diseases, regardless of their underlying pathology, at some point of their progression may have overlapping clinical and pathological phenotypes, for example postural instability, due to the disintegration of common neuronal networks[67]. Future research, making use of animal models or combining Diffusion-tensor MRI imaging and fibertractography with postural and gait analysis, may tackle some of these doubts. In this respect, VPD, despite all inherent clinical doubts, deserves further investigation, as different vascular lesioning may serve as a pragmatic approach to unravel the function of different nucleus and locomotor/postural networks.

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