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Thesis: Hallucinations in Parkinson's disease and Selective Attention impairment

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ABSTRACT

Objective: Hallucinations have been documented as a very common non-motor symptom in the course of Parkinson's disease (PD). Therefore, the exploration of the potential trigger factors has gained an outstanding attention so far. The present study examines whether PD patients, who report having experienced hallucinations or misperceptions, declare specific selective attention deficits.

Methods: We evaluated thirty one patients, in total, with confirmed idiopathic PD, regarding the presence of hallucination or not, using a Greek version of the "University of Miami Parkinson's disease Hallucinations Questionnaire" and then assessed their selective attention and visual perception with Ruff 2 & 7 test and HOOPER plus Judgment of Line Orientation test, respectively.

Results: Between the hallucination-free and hallucination-plus group, none statistically significant difference noted, as far as the selective attention domain was concerned. However, the hallucination-plus group revealed a marginally significant lower performance in the object recognition task (HOOPER) [t (29) =2.02, p=.05). When we further divided the hallucination-plus population in two subgroups (plus minor and plus formed hallucination), once again, the performance of the three groups in the selective attention task was comparable, while the previously noted difference in the object recognition task was obscured [F (2, 28) = 3.01, p=.065]. Interestingly, that new categorisation disclosed a statistically significant lower performance in the position discrimination test on behalf of PD patients with formed hallucination [F (2, 28) = 4.20, p= .025].

Conclusion: Our findings did not reveal impaired selective attention as a potential trigger factor of hallucinations in PD patients, probably because of the sensitivity of our test in a specific form of selective attention. However, our results regarding deficits in visuoperceptive and visuospatial tasks were in agreement with previous studies.

INTRODUCTION

While Parkinson's disease (PD) has originally been described as a motor disorder, with bradykinesia, resting tremor, rigidity, and postural instability, it is now drawing increased attention to associated non-motor symptoms, such as cognitive decline and neuropsychiatric features. Though parkinsonism (i.e. motor symptoms) is the key mark for searching medical assistance initially, it is now believed to be nothing but the *'tip of the iceberg'* of an extremely multifaceted and complex disorder (Langston, 2006).

Among the neuropsychiatric and mental disturbances observed in the course of the disease, visual hallucinations (VH) and illusions or misperceptions are the most common one. They can be present early, even prior to the motor symptoms or the initiation of the treatment with levodopa, and are worsening as the disease progresses and further cognitive decline occurs. According to prospective studies, 10% to 40% of the patients are considered to be affected (Fenelon et al., 2000; Barnes & David, 2001). Hallucinations and other neurobehavioral symptoms provoke such a stress that will contribute to increasing need for care-giving (Fernandez, 2012) and, ultimately, for permanent nursing home placement, which is associated with high mortality rate (Goetz & Stebbins, 1995).

According to the American Psychiatric Association Diagnostic and Statistical Manual, Edition IV-TR, hallucination is "a sensory perception that has a compelling sense of reality of a true perception, but occurs without external stimulation of the relevant sensory organ". The English word "hallucination" originates from the Latin verb *hallucinari*, which means "to wander in the mind." On the other hand, illusion/misperception represents the failure to successfully integrate stimuli that have been physically present (Shine et al., 2011). Although they are accounted for two discrete phenomena, they often overlap or even trigger each other. Visual hallucinations in PD can be divided in two main categories: formed and minor hallucinations (Fenelon, 2008). **Formed** hallucinations are complex, consisting of familiar or unfamiliar persons, and less often animals or objects. **Minor** hallucinations include visual illusions and sense of presence or passage hallucination in the peripheral visual field. The above figures appear suddenly, usually in dim light, whilst patient's eyes are open. They are static or moving, and seem real (Holroyd et al.,

2001). They usually do not disturb the patients, as long as insight is intact. These images are also seen against the background of the existing scene, instead of filling the whole visual field (Barnes & David, 2001).

So far, many risk factors have been incriminated for the occurrence of visual hallucinations (Fenelon, 2008). (a) All anti-parkinsonian agents, and probably dopamine agonists more often than levodopa, can trigger VH. Worth to mention, even high doses of intravenous L-dopa infusion failed to be connected with higher prevalence of hallucinations (Goetz et al., 1998). (b) Cognitive impairment is considered as an independent risk factor, as well as (c) duration of disease. (d) REM sleep disorders are quite common in PD, and their association with VH has been thoroughly studied and established (Goetz et al., 2005). (e) Visual dysfunction in PD patients, significantly modulated by dopamine at retina level (Archibald et al., 2011), and (f) depression are also associated with VH.

Despite extensive studies and attempts to determine the underlying pathophysiological mechanisms of complex hallucinations *in general*, there is still no satisfactory unifying framework. In 2005, Collerton et al. proposed the "Perception and Attention Deficit" (PAD) model in the generation of recurrent complex visual hallucinations (RCVH) in Lewy Body Disease. The subjective perception of the whole visual world was claimed to be a dynamic mutual interaction of the external sensory stimuli, the internal object/scene representation and the goal-directed attention or, otherwise, selective attention. The initial sensory input activates a number of potentially 'seen' photo-objects/images, or modifies those already activated. These 'images' are in a reciprocal competition for further processing (Peterson & Rhodes, 2003). Eventually, bottom-up and top-down information processes will allow one 'image' to rise up and enter consciousness. Attention is considered to play a primary role in the identification of the correct photo-image by increasing the signal to internal noise ratio. However, no isolated impairment either in attention or in perception could independently account for the generation of visual hallucinations (Meppelink et al., 2008).

Hobson initially claimed that any change in the anatomical and neurochemical networks involved in the information processing (A=Activation), the generation of

internal images and interaction with the outside world (I=Input), as well as the overall integration module (M=Modulation), could explain the physiological variants or the pathological states of consciousness. Diederich et al. (2005) used Hobson's three-dimensional state/phase model for consciousness (AIM) while proposing a new integrative model for VH in PD. Specifically, the researchers focused their attention on the imbalance between a weak external input, either because of visual problems or reduced luminance, and the release of mistaken internal images or previously recorded perceptions, in order to complete the defective representation of the external visual scene.

More recently, Shine and his colleagues (Shine et al, 2011, Shine et al, 2014) suggested that visual misperceptions and hallucinations in PD are due to disruption of information processing across the *Attentional Networks*. Normally, the initial process of the visual stimuli in the primary occipital cortex (V1) will further follow the Ventral Visual Pathway ('WHAT' pathway). The salient item will alert the Ventral Attention Network (VAN) – consisting of the anterior insula and the dorsal anterior cingulate cortex – which will interact with the Dorsal Attention Network (DAN) for the content to be identified. The Dorsal Attention Network is composed of projections between the frontal eye fields, the dorso-lateral prefrontal and the posterior parietal cortex. If the interaction between VAN and DAN fails, then the Default Mode Network (DMN) will take over to interpret the potential image by retrieving episodic memories and semantic knowledge. Then again, the Default Mode Network, consisting of the medial temporal, medial prefrontal, posterior cingulate, and lateral parietal cortices, and precuneus – has been already documented to have an abnormal deactivation in PD patients during goal-directed tasks (van Eimeren et al., 2009). Based on that, Yao et al (2014) further explored and confirmed that "relatively higher connectivity in a functionally abnormal DMN, is associated with generation of visual hallucinations".

On the other hand, numerous researchers have also been occupied with the neuropsychological profile of PD patients admitting experience of hallucinations. Results have so far been rather variable. Llebaria et al. (2010), using their specific cognitive scale for PD (PD-CRS), examined sustained attention, which indeed was found significantly varying in patients with either formed or minor VH, or without

VH. Similarly, Koerts et al. (2010) pointed out that 'decreased levels in sustained attention are correlated with a decreased level in object and space perception in PD patients with VH', and concluded that it would be worthwhile to investigate, if other forms of attention, such as selective or divided, were also impaired. Bronnick et al. (2011), with the use of a Computerised Test for assessing attention, found that only the choice reaction time, i.e vigilance, was an independent predictor of hallucinations in *demented* PD patients. On the other hand, Hepp et al. (2013) – using an extensive neuropsychological battery – showed that only Trail Making Test A performance (speed of visuomotor search and scanning) was significantly impaired between groups of patients with and without VH, while other cognitive domains such as visuospatial, executive functions – as tested by the STROOP test – verbal and categorical fluency etc, were comparable.

Focused or selective attention is generally one of the most intensively studied cognitive domains and one of the most sensitive ones. It is the capacity of highlighting only the important stimuli while suppressing awareness of competing distractions. Basically it can be viewed as a protective process against information overload. Bearing in mind all the above, we decided to further examine specifically selective attention in PD patients with hallucinations. We chose to use a simple pencil-paper test, the "Ruff 2&7 selective attention test", which does not require significant memory load or intact colour discrimination ability, unlike the Digit Symbol Modality Test or the STROOP test. We were also keen to investigate if selective attention is more impaired among patients with formed rather than minor hallucinations.

METHOD

Participants

Thirty-one non-demented patients, clinically diagnosed with idiopathic Parkinson's disease, were included in the current study. All participants were attending the PD outpatient clinic of the Neurology department of Aeginition hospital, and agreed to be further evaluated for potential occurrence of hallucinations and engage to a brief neuropsychological assessment. Overall nineteen patients were classified as having experienced hallucinations within the last one month (PD+H) (ten reported formed hallucinations/PD+Hformed and nine of them only minor hallucinations/PD+Hminor) and twelve patients as never having experienced any kind of hallucinations (PD–H).

Exclusion criteria for the present study were: 1) diagnosis of dementia and/or a score of less than 24 in Mini Mental State Examination, b) concurrent neurological or neurodegenerative disease, i.e. stroke, epilepsy, c) history of mental disorder, other than depression, as classified in DSM-IV-TR, and d) severe visual impairment – clinically assessed visual acuity less than 50% or 20/200, using the Rosenbaum Pocket Vision Screening Card.

Procedure and materials

All patients were seen by neurologists specialised in Movement Disorders, who provided medical records on onset symptoms and form of disease, as well as, clinical scores for motor severity and disease staging (UPDRS part III and Hoehn & Yah) on that date.

To allow a comprehensive assessment of the presence and type of hallucinations, we used a Greek version of the "University of Miami Parkinson's disease Hallucinations Questionnaire" (UM-PDHQ) (Papapetropoulos et al., 2008). This questionnaire is composed of 6 quantitative items (range 0-14) and 14 qualitative items. The first item is a gating question for the presence or absence of hallucinations, whilst the others evaluate the modality, frequency, duration, insight, and emotional burden. In the qualitative section, descriptive information for these experiences is collected, and anti-parkinsonian medications and dosages are documented.

A levodopa-equivalent daily dose score (LEDD) was calculated for all patients, according to the conversion formulae that was published by Tomlinson et al., in their literature review in 2010. The LEDD of a drug is defined as the value that can produce the same symptomatic control as 100mg of immediate release levodopa-combined with dopa-decarboxylase inhibitor.

The Mini Mental State Examination Test (Folstein & McHugh, 1975) was first administered, as a screening test for participants' general cognitive function. We further continued assessing visual selective attention using:

The **Ruff 2 and 7 Selective Attention Test/ Ruff 2&7** (Ruff et al., 1992). This is a simple pencil-and-paper test, which requires participant to detect and cross out the

digits 2 and 7, either among blocks of capital letters of Latin alphabet, or among blocks of digits, i.e. assesses the ability to select relevant stimuli, while ignoring irrelevant ones. Each block, consisting of three lines, needs to be scanned from left to right. The participant is being told that after a brief time (fifteen seconds), the examiner will say 'Next' and the participant has to start a new block – time allowed for the whole test (ten blocks) is five minutes. To score this test, we used raw scores of hits as *Speed measurement* (Automatic Detection Speed/**ACS**, when targets were presented among letters, Controlled Search Speed/**CCS**, when targets were presented among digits, and Total Speed/**TS**, for the whole session), and raw quotient of hits over hits plus errors of omission and commission, as Accuracy measurement (Automatic Detection Accuracy/**ADA**, Controlled Search Accuracy/**CSA** and Total Accuracy/**TA,** respectively). Total speed and accuracy values represent a measure of sustained attention (five minutes).

We also documented patients' visuospatial function, in order to provide information regarding their ability for object recognition and position discrimination. Therefore, we gave two more tests:

1. The **Hooper Visual Organizational Test/ HVOT** (Hooper, 1952). It consists of 30 black-and-white drawings of common objects and animals that have been cut off in two or more pieces, requiring mental rotation to identify each item. We presented the items in the order modulated for Greek population (Giannakou & Kosmidis, 2006), and scored responses with full or half credit as per Greek manual (maximum score = 30).
2. The **Judgment of Line Orientation test/JLO** (Benton et al., 1983), short form of ten items (pairs) from the standard JLO, with five examples preceding. It is a commonly used test to measure visuospatial perception. Two lines are presented at the top page and a standard fan-shaped array of eleven numbered lines at the bottom. The examinee needs to identify the two lines from the bottom and match the angles of the two lines at the top (maximum score= 20).

Neither HOVT, nor JLO are time limited tests. However, the participant is advised to respond spontaneously, and as fast as possible, presuming that the initial answer is more likely to be accurate.

STATISTICAL ANALYSIS

All analyses were performed with the IBM Statistical Package for Social Sciences 21.0. Level of statistical significance was set at $p < .05$. Demographic characteristics, clinical data, as well as, scores from the neuropsychological tests of PD-H and PD+H groups were compared either with parametric Student's t-test for independent samples (numerical variables) or non-parametric chi-square test (gender distribution). Due to the small number of participants, data were normally distributed and therefore parametric statistics were allowed.

We then divided the group of PD patients with hallucinations in two subgroups: 1) those who reported formed hallucinations (PD+H formed) and 2) those who reported only minor (PD+H minor). We proceeded to this discrimination, based on the answers given to the qualitative section of the main questionnaire. We did so in order to examine if there was any clinical or demographic difference in favour of the presence as well as the type of hallucination. The scores of neuropsychological tests between the three groups (PD-H, PD+ H minor and PD+ H formed) were further compared using analysis of variance (ANOVA).

RESULTS

The two groups (hallucination free and hallucination plus) did not differ in regard to age, education and general cognitive function (MMSE), as per Table 1. Additionally, no difference was noted according to their motor status documented as UPDRS Part III score [$t(28) = -.861$, $p=.40$]. Overall they were well matched, including the Levodopa equivalent daily dose (LEDD).

Table1. Demographic and clinical characteristics for PD patients without (PD-H) and with (PD+H) hallucinations (t-test and chi-square test).

	PD-H (n=12)		***PD+H (n=19)***		***p value***
Age					
Mean(SD)	64.45	(10.51)	68	(9.59)	ns
Range	47-82		52-83		
Education (years)					
Mean(SD)	14	(4.12)	9.5	(3.72)	ns
range	6-20		4-16		

MMSE					
Mean(SD)	29	(1.34)	27.75	(1.35)	ns
Range	17-30		26-30		
Diseas.duration(y)					
Mean(SD)	6.59	(4.99)	5.83	(4.95)	ns
range	1-17		4-14		
LEDD					
Mean(SD)	654.67	(568)	563.69	(376.39)	ns
range	100-1697		154-1410		
UPDRSiii					
Mean(SD)	7.82	(11.2)	10.50	(9.68)	ns
range	1-33		2-33		
H&Y					
Mean(SD)	2.05	(0.75)	2.42	(0.51)	ns
range	1-3		2-4		
Male	8	(66.7%)	9	(47.4%)	ns
Female	4	(33.3%)	10	(52.6%)	ns

ns: non significant

Analysing the scores of the neuropsychological tests between the two groups , as per Table 2, the only marginally significant difference that was noted, was the one referring to the performance in the object recognition task (HOOPER) [t (29) =2.02, p=.05].

Table 2. Performance in the neuropsychological tests- two groups (t-test).

	PD-H (n=12)		***PD+H (n=19)***		***p value***
	Mean	**(SD)**	**Mean**	**(SD)**	
Ruff 2&7					
ADS	85.33	(23.85)	73.32	(20.09)	ns
ADA	94.85	(4.43)	93.87	(6.78)	ns
CSS	81.33	(23.61)	68.58	(17.29)	ns
CSA	93.06	(2.75)	91.06	(7.84)	ns
TS	166.67	(46.75)	140.16	(39.39)	ns
TA	94.17	(3.06)	92.16	(6.85)	ns
HOOPER	**18.91**	**(4.05)**	**15.52**	**(4.83)**	**.05**
JLO	16.92	(1.62)	15.63	(2.89)	Ns

With the use of the Hallucinations Questionnaire we further divided the hallucinations-plus group in those with minor and those with formed ones. This was

based on the subjective impression of the examiner, who categorised the given information according to the standard terminology. Patients answering the structured interview were further encouraged to speak freely about their seen-'images', in order to provide as much reference as possible. In Table 3, demographic and clinical characteristics of the three groups are shown. They were well matched for age, education and disease stage. Unsurprisingly, the group with formed hallucinations (PD+H formed) reported that hallucinations were more frequent [t (17) =2.27, p=.036] and overall more severe [t (17) =3.45, p= .003] than the minor hallucinations' group. Both subgroups appeared to retain insight of those experiences.

Table 3. Demographic and clinical characteristics for the three groups (one-way ANOVA and t-test for those variable where there were NA values for hallucination-free group).

	PD-H (n=12)		***PD+Hminor (n=9)***		***PD+Hformed (n= 10)***		***p value***
Age							
Mean(SD)	64.45	(10.51)	68.14	(11.05)	67	(7.72)	ns
range	47-82		52-83		56-77		
Education (years)							
Mean(SD)	14	(4.12)	9.71	(4.38)	10.17	(3.6)	ns
range	6-20		4-16		6-15		
MMSE							
Mean(SD)	29	(1.34)	27.86	(1.67)	27.83	(0.98)	ns
range	17-30		26-30		26-29		
Duration(y)							
Mean(SD)	6.59	(4.99)	5.29	(5.35)	7	(4.23)	ns
range	1-17		4-15		3-14		
LEDD							
Mean(SD)	654.67	(568.51)	614.89	(372.23)	517	(393.97)	ns
range	100-1697		154-1182		200-1410		
UPDRSiii							
Mean(SD)	7.82	(11.2)	5.57	(4.35)	17.67	(10.13)	ns
range	0-33		1-12		2-33		
H&Y							
Mean(SD)	2.05	(0.75)	2.21	(0.27)	2.67	(0.6)	ns

Frequency						
Mean (SD)	**N/A**	**1.71**	**(1.6)**	**3.5**	**(0.55)**	**.036**
Insight						
Mean (SD)	N/A	0.57	(0.79)	0.83	(0.75)	ns
Severity						
Mean (SD)	**N/A**	**3.86**	**(1.77)**	**7.33**	**(1.63)**	**.003**

N/A: non applicable

frequency: 0= occasionally, 1=<1/week, 2=~1/week, 3=frequently,>2/week, 4=very frequently, >1/day

insight: 0=not real, 1= sometimes real, 2=always real

severity: min=0, max=14

According to Table 4, the performance of the three groups in the Ruff 2 & 7 selective attention test was comparable and no significant difference was noted. Worth mentioning that in contrast to our previous comparison, where PD hallucination-free and PD hallucination-plus group differed in the HOOPER Visual Organizational Test, this statistically significant result was not retained after dividing the PD plus hallucination population into the subgroups (minor and formed), [F (2, 28) = 3.01, p=.065]. Nevertheless, with this categorisation, the three groups scored significantly differently in the position discrimination test/JLO [F (2, 28) = 4.20, p= .025].

Table 4. Performance in the neuropsychological tests- three groups (one –way ANOVA).

	PD-H (n=12)		***PD+Hminor (n=9)***		***PD+Hformed (n= 10)***		***p value***
	Mean	**(SD)**	**Mean**	**SD**	**Mean**	**SD**	
Ruff 2 & 7							
ADA	85.33	(23.85)	76.67	(25.67)	70.30	(14.16)	ns
ADS	94.85	(4.43)	92.95	(9.33)	94.70	(3.61)	ns
CSS	81.33	(23.61)	72.44	(21.25)	65.10	(12.96)	ns
CSA	93.06	(2.75)	92.39	(9.62)	89.87	(6.11)	ns
TA	166.67	(46.75)	145.44	(51.55)	135.40	(26.23)	ns
TS	94.17	(3.06)	91.9	(9.05)	92.40	(4.59)	ns
HOOPER	18.91	(4.05)	14.06	(4.56)	16.85	(4.91)	ns (.065)
JLO	**16.92**	**(1.62)**	**17**	**(2.45)**	**14.4**	**(2.80)**	**.025**

Applying the Tukey criteria in post-hoc analysis, we noted that the difference was preserved between the hallucination-free and the hallucination-plus formed group, as well as, between the hallucination-plus minor and the hallucination-plus formed group (Table 5). The hallucination-free and hallucination-plus minor group did not differ in any of the scores in the neuropsychological assessment.

Table 5. Post-hoc analysis with Tukey criteria for JLO, only.

	Halluciantion	*Hallucination*	*P value*
JLO	none	minor	Ns
		formed	**.041**
	minor	formed	**.05**

DISCUSSION

Reviewing the literature on PD with and without hallucinations, we came across variable cognitive deficits. This variability might be due to differences in sample size, medication/ LEDD or test options. In the current study, we assessed a random sample of patients attending an outpatient clinic during routine visits in regard to potential experience of hallucination, based on an extended questionnaire. Our aim was to further examine whether there were specific deficits in visual selective attention and if these could be associated with different types of hallucinations.

Despite the small sample there was an acceptable match between the groups for demographic and clinical characteristics. Initially, we compared the PD hallucination-free and PD hallucination-plus group for Ruff 2 & 7 test performances. No significant difference was recorded. Ruff 2 & 7 is an easily administered task assessing the speed and accuracy of information processing. Regardless of the numerically lower performance of the PD+H patients, the presence of visual hallucinations was not a sensitive index that could affect their ability of self-pacing target selection among the distracters (letters or digits). When we further subdivided the hallucination-plus group in plus-minor or plus-formed hallucination patients, selective attention did not differ at all between the three populations.

That was an unexpected result, as previous studies having shown that hallucinations and misperceptions are strongly associated with disrupted processing in attentional networks (Shine et al, 2012). More specifically, Zhou et al (2012) reported that PD patients showed a selective abnormality in the orienting network, i.e. the selection of information among numerous sensory inputs. We should highlight that only non demented PD patients with preserved cognitive reservoir were included in our study, and the vast majority of those with hallucinations were retaining insight of their

experience. We therefore assume that hallucinations in PD do not seem to influence their performance in selective attention task, because patients appear to be aware of them, recognise and accept them as part of their disease, in contrast to schizophrenic hallucinations where patients get disorganised and "believe" them.

We underline the absence of difference of LEDD between hallucination-plus and hallucination-free group, in agreement with previous studies and in favour of the conclusion that there is no dose effect relationship between dopaminergic treatment and presence and/ or severity of hallucinations (Fenelon et al, 2008). In other words, despite the noticeably higher LEDD in the hallucination-free group included in this study, these patients were not 'suffering' such an unpleasant experience.

Patients who self-reported hallucinations recognised marginally significantly fewer objects in HOOPER than the non-hallucinators, fact that is consistent with previous work (Meppelink et al., 2008). The Hooper Visual Organisation Test is an excellent measure of visual perception, but has also elements of visual confrontation naming and executive function. To name the object presented in scattered pieces it is necessary to initially detect a salient element of it and figure it out as fast as possible. We subjectively observed that PD patients with hallucinations were able to quickly distinguish the salient (for example: the rabbit ears or sails of sailing boat) but not effectively retrieve the correct image. Interestingly, progressive cortical thinning has been reported in areas functionally specialised in visuoperceptive integration (Pagonabarraga et al., 2013).

Visuospatial ability of PD patients with formed hallucinations was significantly impaired, compared to the hallucination-free or even the minor hallucination-plus group. Those patients were less successful in detecting the right angle position of the presented lines, as if they had difficulties in imaginary spatial representation. Using MRI, Ramirez-Ruiz et al. (2007) documented that PD patients with visual hallucinations had gray matter volume depletion in the lingual gyrus and superior parietal lobe, areas responsible for visuospatial perception.

In conclusion, our study failed to reveal impaired selective attention as a potential trigger factor of hallucinations in PD patients. There are supposedly various forms of

selective attention and our examination was probably sensitive in only one type; other tests could assess other forms of selective attention and could detect such deficits. Even though our groups were fairly matched, a small sample size increases the risk for a type II error. Potential relationship between clinical characteristics, such as handedness, laterality or type of onset with presence of hallucinations and performance of patients in visuoperceptive and visuospatial tasks, should be further explored where statistically significant differences were noted (i.e in HOOPER and Judgement of Line Orientation/JLO tests).

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