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1 **Title:**

2 Effects of Levodopa on Vividness of Motor Imagery in Parkinson Disease

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6 **Running Title:**

7 Motor Imagery “Off” anti-Parkinson medication

8 **Keywords:**

9 Parkinson’s Disease, Motor Imagery, Levodopa, KVIQ

10

11 **Abstract**

12 **Introduction:** Motor imagery during functional magnetic resonance imaging is
13 commonly used to understand the neural underpinnings of complex movements. This
14 approach has recently been applied to individuals with Parkinson disease (PD) to better
15 understand how brain function may relate to movement dysfunction. However, the
16 ability of individuals with PD to imagine movements when “Off” dopamine replacement
17 medication is poorly understood. Therefore, the primary purpose of the current study is
18 to test the ability of people with PD to imagine movements while “On” and “Off” anti-
19 Parkinson medication.

20 **Methods:** Vividness of imagery was assessed in 28 individuals with mild to moderate
21 PD (Hoehn and Yahr stages 1-3) via the Kinesthetic Visual Imagery Questionnaire
22 (KVIQ-20) both “On” and “Off” anti-Parkinson medication. Vividness of imagery of 32
23 age-matched older adults was also assessed.

1 **Results:** No differences in vividness of imagery were observed between “Off” and “On”
2 medication states ($p=0.15$). Imagery was similar between controls and PD both “Off”
3 ($p=0.25$) and “On” ($p=0.46$) anti-Parkinson medication. A significant correlation was
4 observed between imagery and disease severity while “On” anti-Parkinson medication
5 ($r= -0.49$; $p=0.008$).

6 **Discussion and Conclusions:** Vividness of movement imagery was not different
7 between “Off” and “On” anti-Parkinson medications or between PD and controls. These
8 results suggest that people with PD are able to imagine similarly to older adults both
9 when “On” and “Off” anti-Parkinson medication, and supports the use of motor imagery
10 in the “Off” medication state.

11

1 INTRODUCTION

2 Motor imagery (MI) is “a dynamic state during which representations of a given
3 motor act are internally rehearsed in working memory without any overt motor
4 output”[1]. MI has been used extensively with imaging techniques such as functional
5 magnetic resonance imaging to provide insight into the neural underpinnings of complex
6 motor processes in healthy adults [2-8]. More recent studies have begun to use MI with
7 imaging techniques to better understand how brain pathology in individuals with
8 Parkinson disease (PD) relates to movement dysfunction [7,9-11]. In these
9 investigations, PD subjects are often studied “Off” anti-Parkinson medication (Levodopa
10 replacement). However, the ability of people with PD to imagine movements while “Off”
11 dopamine replacement medication is not well understood. One recent investigation
12 showed that individuals with PD have similar vividness of imagery as healthy adults
13 [12]; however, this study tested the vividness of imagery in people with PD while “On”
14 anti-Parkinson medication. Levodopa has been suggested to normalize brain activity in
15 PD in many regions, including the supplementary motor area (SMA) [13-16]. This region
16 is associated with motor planning [17,18] and has been shown to be active during both
17 overt [15] and imagined [4,7] movements. Therefore, pathological activation of SMA, as
18 well as other regions, may reduce the ability of this group to imagine movement in the
19 “Off” medication state. As imagery studies are often carried out with patients “Off” anti-
20 Parkinson medications, it is important to determine the degree to which people with PD
21 can imagine in this medication state. Further, MI has shown promise as a rehabilitative
22 strategy in both healthy individuals [19], and recently, those with neurological disorders,
23 specifically stroke [20,21]. Though rehabilitative MI has not yet been tested in those with

1 PD, understanding changes in imagery while “Off” and “On” anti-Parkinson medication
2 could provide insight into which medication state is better suited for this potential
3 intervention.

4 The purpose of the current study was to test vividness of MI in individuals with
5 PD both “On” and “Off” anti-Parkinson medications, as well as how vividness of MI in
6 those with PD compares to healthy older adults. Due to the altered activation of brain
7 regions (including the SMA) thought to be associated with motor planning while “Off”
8 anti-Parkinson medication, our primary hypothesis is that individuals with PD “Off” anti-
9 Parkinson medication would exhibit worse vividness of imagery with respect to “On”
10 medication, and that the normalizing effects of Levodopa would result in similar imagery
11 scores between PD “On” and healthy controls. Our secondary hypothesis is that more
12 severe PD symptoms will be associated with worse MI.

13

14 **MATERIALS AND METHODS**

15 **Participants**

16 Twenty eight individuals with PD (17 male) and 32 age-matched healthy older
17 adults (16 male) participated in the study. Six PD and 2 controls were left handed based
18 on self report. Thirteen of 28 PD presented with unilaterally increased motor symptoms
19 on their left side, 14 were more affected on the right side and 1 was equally affected
20 bilaterally. Among those with PD, four individuals exhibited dyskinesia. Twenty-four of
21 the 28 subjects exhibited tremor. Exclusion criteria included severe orthopedic problems
22 of upper or lower limbs, deep brain stimulation, and any neurological disorders other
23 than PD. Diagnosis of PD was given by a board certified neurologist using the

1 diagnostic criteria for “definite PD” [22] and based on established criteria [23]. All
2 individuals with PD were taking levodopa (Mean \pm SD Levodopa Equivalent Daily
3 Dose=928 \pm 566; range 300-3000) when enrolled in the study. Written informed consent
4 was provided by all subjects in accordance with the Helsinki Declaration of 1975, and all
5 procedures were reviewed and approved by the Human Research Protection Office at
6 Washington University School of Medicine.

7 **Quantifying Imagery**

8 To assess imagery ability, the Kinesthetic Visual Imagery Questionnaire (KVIQ-
9 20) was administered to all subjects in a similar manner to that described in Malouin et
10 al [24]. The KVIQ-20 was chosen as it was designed specifically to be administered to
11 individuals with movement disorders [24], and has previously been shown to be reliable
12 for individuals with PD [25]. In addition, the ease and speed of administration of this test
13 make it attractive as a potential tool to screen for ability to imagine.

14 The KVIQ-20 includes 10 motions of the neck, shoulders, upper limb, lower limb,
15 and trunk. To administer the KVIQ-20, each motion is demonstrated by the tester, and
16 then completed by the participant. The participant then imagines the motion and rates
17 the vividness of his visual imagery followed by the vividness of his kinesthetic imagery,
18 each on a 5 point scale (5=image or intensity as vivid as completing the motion; 1= no
19 image or sensation). Visual imagery represents the clarity of the image, and kinesthetic
20 imagery represents the sensation of motion while imagining the task. Each score is
21 recorded by the examiner.

1 Seven of the 10 motions consist of movement of a single limb. For these
2 motions, imagery of both the left and right sides were assessed. Within each task, the
3 left side was assessed first, followed by the right.

4 Kinesthetic and visual scores were calculated as the sum of scores from each
5 motion, with scores from bilateral motions averaged across left and right sides giving a
6 minimum possible score of 10 and a maximum possible score of 50 (10 motions x
7 maximum rating of 5). KVIQ-Total scores were determined as the sum of kinesthetic
8 and visual sub-scores (maximum possible score = 100).

9 To assess within-subject side differences, scores were compared across more
10 and less affected sides (PD) and across dominant and non-dominant sides (PD,
11 control). Differences across more and less affected sides in PD were assessed for 27
12 subjects, as one individual showed similar dysfunction across sides. These unilateral
13 scores were calculated as the sum of kinesthetic and visual scores for one side (more
14 affected, less affected, dominant, or non-dominant) across all bilateral movements. As
15 there are 7 movements where both sides are measured, with a maximum KVIQ score of
16 10 for each movement (max kinesthetic score =5; max visual score = 5), the maximum
17 possible score for KVIQ-Unilateral is 70. For individuals with PD, more and less affected
18 side was determined by summing unilateral components of the part III subscale of the
19 Movement Disorders Unified Parkinson Disease Rating Scale (MDS-UPDRS III [26]).
20 The side which accumulated a larger score was deemed the more affected side. No
21 differences were observed in KVIQ-Unilateral scores across dominant or non-dominant
22 (PD, control), or more or less affected (PD) sides (See Results; Figure 1),

1 The KVIQ was administered by one of two trained individuals. Both individuals
2 were trained to administer the exam, and given a script to follow to reduce variance in
3 instruction to participants. For an individual with PD, the “Off” and “On” medication
4 testing sessions were always administered by the same tester. Due to the scripted test
5 administration, as well as the fact that ratings reported by the subject are not open to
6 tester interpretation, we are confident that testing was consistent across testers.

7 Individuals with PD were tested two times, while healthy controls were tested
8 once. Individuals with PD were first tested “Off” anti-Parkinson medication (>12 hours
9 since last dose; a commonly used criterion used to assess PD symptoms “Off”
10 medication [7,9-11,27]). After taking a normal dose of medication, subjects waited for
11 approximately one hour, and the KVIQ-20 was administered again. Approximately 2
12 hours elapsed between KVIQ-20 testing sessions for individuals with PD.

13 Subjects’ disease severity was assessed by the MDS-UPDRS III and the Hoehn
14 and Yahr scale [28] both “On” and “Off” medication.

15 **Statistics**

16 Imagery scores for both groups were shown to be normally distributed (non-
17 significant Skewness and Kurtosis) and have approximately equal variance (non-
18 significant Levene’s test) across groups. Therefore, parametric tests were used for all
19 analyses. Paired t-tests were used for all within-subject comparisons: ie: comparison of
20 within-subject kinesthetic and visual scores; effects of medication on KVIQ-Total scores,
21 UPDRS scores, and Hoehn and Yahr staging in those with PD. Independent t-tests
22 were used for across group comparisons: i.e., vividness of MI across groups, and age
23 across groups. To determine whether motor severity predicts one’s ability to imagine,

1 Pearson correlation coefficients were used to assess the relationship between KVIQ
2 scores and motor severity (MDS-UPDRS III and Hoehn & Yahr scale) both “On” and
3 “Off” anti-Parkinson medication. All measures are noted as mean \pm standard deviation,
4 unless otherwise noted.

5

6 **RESULTS**

7 Individuals with PD were of similar age as healthy controls (PD=71.0 \pm 8.9;
8 Controls=70.3 \pm 10.6; p=0.78). Individuals with PD improved MDS-UPDRS III and Hoehn
9 & Yahr scores after administration of anti-Parkinson medication (p<0.001 and p=0.01,
10 respectively; Table 1), suggesting subjects did see significant benefit from their anti-
11 Parkinson medication.

12 Similarly to previous investigations [12], no differences in KVIQ-Unilateral scores
13 were observed between dominant and non-dominant limbs for control (p=0.34), PD “Off”
14 (p=0.06), or PD “On” anti-Parkinson medication (p=0.22). In addition, within the PD
15 group, no differences were observed in KVIQ-Unilateral between more and less affected
16 limbs “Off” (p=0.13) or “On” (p=0.78) anti-Parkinson medication (Figure 1).

17 Contrary to our primary hypothesis, there were no statistically significant
18 differences in KVIQ-Total in people with PD when “Off” or “On” anti-Parkinson
19 medication (Table 1). Further, no differences were observed between KVIQ-Total in
20 healthy older adults and individuals with PD “On” or “Off” anti-Parkinson medication.
21 Kinesthetic and visual KVIQ components were also not different between PD “On” and
22 controls or PD “Off” and controls. Across all subjects, the visual component of the KVIQ-
23 20 was significantly higher than kinesthetic component of the KVIQ-20 score (p<0.001).

1 Higher scores on the visual imagery with respect to kinesthetic imagery were also
2 shown in those with PD while both “On” ($p=0.006$) and “Off” ($p=0.013$) anti-Parkinson
3 medication.

4 Six of 32 control subjects and five of 28 PD subjects exhibited scores of <20 on
5 either visual or kinesthetic components of the KVIQ-Total. These PD subjects exhibited
6 KVIQ scores <20 both “On” and “Off” medication. A score of 20 represents an average
7 response of 2 across all tasks, or a “blurred image” and “mildly intense” for visual and
8 kinesthetic imagery, respectively.

9 Scores on the KVIQ-Total while “On” anti-Parkinson medication were positively
10 correlated to KVIQ-Total scores “Off” anti-Parkinson medication ($r=0.94$, $p<0.0001$;
11 Figure 2a). In partial support of our secondary hypothesis, KVIQ-Total scores “On”
12 medication were negatively correlated to MDS-UPDRS III “On” medication ($r=-0.49$,
13 $p=0.008$; Figure 2b) such that increased disease severity predicted worse imagery.
14 MDS-UPDRS III “Off” medication was not, however, correlated to KVIQ-Total “Off”
15 medication ($r=-0.31$, $p=0.11$; Figure 2c). Finally, no relationships were observed
16 between KVIQ-Total score and age for PD ($r=-.26$, $p=0.18$), control ($r=-0.05$, $p=0.81$) or
17 the combination of PD and control subjects together, ($r=-0.14$, $p=0.28$; Figure 2d).

18

19 **DISCUSSION**

20 Dopamine replacement therapies have been shown to be beneficial for reducing
21 many of the symptoms of PD [29]. Until now it has been unclear whether dopamine
22 replacement impacts MI in people with PD. As many imagery studies are carried out
23 with individuals “Off” anti-Parkinson medication, it is critical to determine the degree to

1 which individuals with PD can imagine movement while in the “Off” anti-Parkinson
2 medication state. Our results suggest that in both the “Off” and “On” medication states,
3 individuals with PD have similar imagery vividness as healthy older adults. This result
4 provides support for MI testing while people with PD are “Off” anti-Parkinson
5 medication. Further, MI has been suggested as a rehabilitative strategy for individuals
6 with neurological disorders [20,21]. The ability of individuals with PD to imagine “Off”
7 their anti-Parkinson medication suggests this potential rehabilitative strategy may be
8 applicable when subjects are “Off” anti-Parkinson medication state.

9 Our results generally fit well with previous reports on MI in individuals with PD
10 [12,25] and healthy older adults [24]. Two recent studies have measured imagery
11 vividness among individuals with PD using the KVIQ-20 while “On” anti-Parkinson
12 medication [12,25]. Randhawa and colleagues (2010) reported vividness of MI of
13 individuals with PD were slightly higher (better) than those reported in the current study.
14 However, this may be due to the fact that subjects in the current study exhibited more
15 severe Parkinsonian symptoms (higher MDS-UPDRS III scores) than those of
16 Randhawa and colleagues. Indeed, correlation results from the current study suggest
17 the possibility that worse MDS-UPDRS III scores may predict worse imagery in PD.
18 Heremans et al. (2011) reported KVIQ-20 values for people with PD “On” anti-Parkinson
19 medications as well as healthy adults to be worse than those reported in the current
20 study. However, similarly to Heremans and colleagues, we observed no differences in
21 vividness of imagery between older adults and individuals with PD while “On” anti-
22 Parkinson medication. Our results further extend the findings of both Heremans &

1 Randhawa, showing that even when “Off” medication, individuals with PD seem to
2 retain the ability to imagine movements.

3 Vividness of imagery “On” and “Off” anti-Parkinson medication was highly
4 correlated, suggesting it was quite consistent across medication states. We also found a
5 medium [30] correlation between MDS-UPDRS III “On” and KVIQ-Total “On” scores,
6 such that individuals with worse MDS-UPDRS III scores had worse KVIQ-Total scores.
7 This correlation suggests that ability to imagine may be related to PD motor symptom
8 disease severity. Our investigation included only individuals with mild or moderate PD.
9 Further studies determining ability of individuals with moderate to severe PD are
10 necessary to better understand how PD severity may be related to vividness of imagery.

11 Across all subjects, age was not correlated with MI. This is consistent with a
12 previous assessment of vividness of imagery across age groups [31] which also showed
13 age not to have a significant effect on MI. Studies assessing different aspects of
14 imagery, such as timing of imagery, have, however, described age-related differences in
15 the ability to imagine movements [32-34]. For example, Personnier and colleagues
16 showed that when imagining gait, older adults systematically over-estimated the
17 duration of imagined movements with respect to overt motions [33]. Together, these
18 results suggest some aspects of MI (timing of imagery) may be altered across age while
19 others (vividness of imagery) seem to be retained.

20 Both PD and control subjects in the current study scored higher on visual
21 components of imagery than kinesthetic components. This result is similar to several
22 previous reports [12,24,35,36], and suggests that like healthy controls [24] and
23 individuals who have experienced a stroke [36], individuals with PD more vividly

1 imagine the visual component of movement than the kinesthetic component. Further,
2 results of the current study show that this relationship is maintained while “Off”
3 medication. That is, visual scores tend to be greater than kinesthetic scores both “On”
4 and “Off” anti-Parkinson medication.

5 Several subjects, both control and PD, demonstrated a marked inability to
6 imagine movement (<20 on either Kinesthetic or Visual components of KVIQ). However,
7 the proportion of individuals who were unable to imagine were similar in control (6/32;
8 19%) and PD groups (5/28; 18%). This is in conjunction with previous reports, which
9 show a small population of both healthy controls [24] and those with PD [12,25] to
10 exhibit poor imagery ability. Subgroup analyses were conducted to determine if subject
11 characteristics in PD (UPDRS, Hoehn and Yahr, disease duration, and age) and
12 controls (age) were different in those exhibiting low imagery scores. In conjunction with
13 correlational analyses described earlier, UPDRS “On” medication was significantly
14 higher (worse) in the group with low imagery scores with respect to others with PD.
15 However, no other differences were observed in those with low KVIQ scores. Due to the
16 similar proportion of poor imaginers in both groups, data from these subjects were not
17 omitted from analysis. These results underscore the importance of assessing imagery
18 ability in all individuals completing a task requiring MI.

19 **Limitations**

20 In the current study it was not possible to counter-balance the order of testing
21 sessions for individuals with PD. That is, participants with PD were always tested “Off”
22 medication first, then again “On” medication. It is therefore possible that “On”
23 medication scores may have been biased due to a practice effect. If this were the case

1 we may expect an overestimation of imagery vividness on the second administration
2 when “On” medication. Despite the possibility of an overestimation of imagery vividness
3 while “On” medication, we still found no differences between “Off” and “On” medication
4 testing sessions, suggesting that “Off” medication imagery is likely not diminished with
5 respect to imagery in the “On” anti-Parkinson medication state. Though the KVIQ was
6 only administered one time to healthy older adults, the similarity in results from the “On”
7 and “Off” medication PD groups suggests there likely would not have been significant
8 changes across multiple testing sessions. In addition, Moulin et al (2007) also assessed
9 the change in score across multiple testing sessions in controls, showing little change in
10 score across sessions [24].

11 The lack of significance when “Off” and “On” anti-Parkinson medication in those
12 with PD could be due to an insufficient sample of PD subjects. Our data suggest that on
13 average, those with PD show an approximately 2.3% increase in KVIQ-Total score (2.3
14 point increase on a 100 point scale) while “On” anti-Parkinson medication with respect
15 to “Off” medication. This corresponds to an effect size of 0.10. Although it is currently
16 unclear what a clinically significant change in KVIQ score may be, we feel that this does
17 not represent a meaningful change in KVIQ score, and therefore are confident that
18 medication did not result in improved MI.

19 We determined the vividness of imagery in people with mild to moderate PD
20 (Hoehn & Yahr stages 1-3). In addition, we showed that while “On” medication, imagery
21 (KVIQ-20) was negatively correlated to disease severity (MDS-UPDRS III). It is possible
22 that our results do not extrapolate to individuals with more severe PD. It therefore

1 remains to be determined whether individuals with severe PD and/or cognitive deficits
2 are able to effectively imagine movement.

3 **Conclusions**

4 Imagery scores while “On” anti-Parkinson medication and after refraining from
5 medication for a commonly used period of time (12 hrs) were both similar to healthy
6 adults, suggesting anti-Parkinson medication likely does not have a substantial effect on
7 vividness of motor imagery for individuals with mild to moderate PD. Although vividness
8 of imagery does not seem to be affected by medication levels, the negative correlation
9 between UPDRS and KVIQ in the “On” state suggests the possibility that imagery may
10 be degraded in individuals with more severe PD. Further research on individuals with
11 more severe PD is necessary to more fully understand this relationship.

12

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19 financial or otherwise, related to the submitted manuscript or the associated research.

20

1 **Running Title:**

2 Motor Imagery “Off” anti-Parkinson medication

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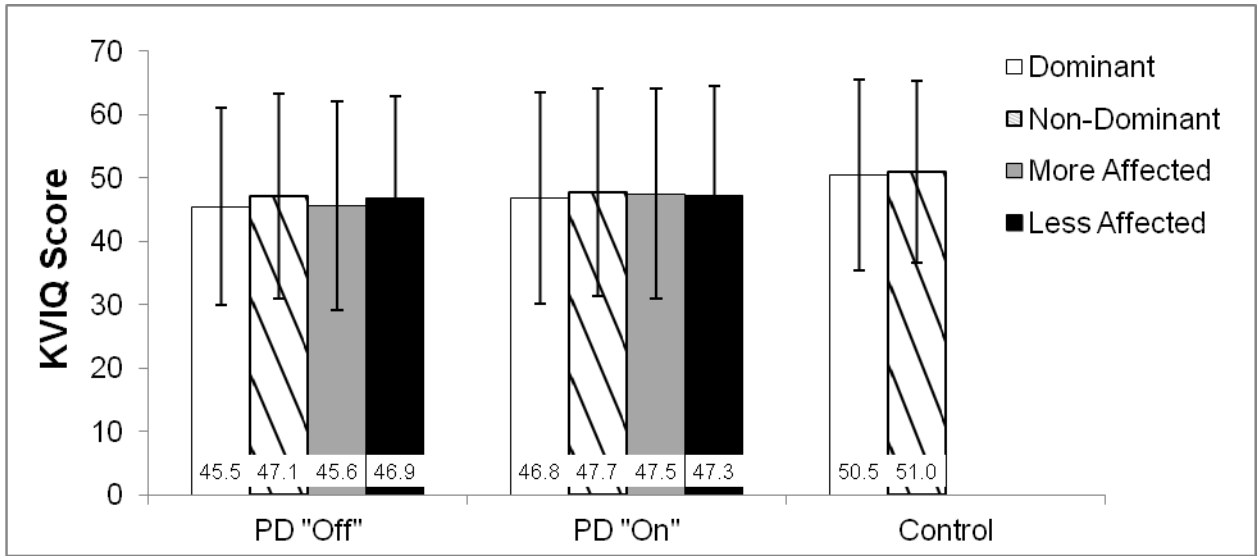
1 Table 1: Demographic and imagery results across groups

Variable	Control (N=32)	PD "Off" (n=28)	PD "On" (n=28)	*P-value: PD "On" vs. PD "Off"	#P-value: PD "Off" vs. Control	#P-value: PD "On" vs. Control
Age	70.3 (10.6)	71.0 (8.9)		-		0.78
Disease Duration	-	6.5 (3.8)		-		-
UPDRS-MDS III	-	37.6 (9.9)	26.6 (9.8)	<0.001	-	-
Hoehn & Yahr Stage	-	2.4 (0.3)	2.2 (0.4)	0.005	-	-
KVIQ - Visual	38.6 (10.9)	34.6 (10.9)	36.3 (11.6)	0.13	0.16	0.42
KVIQ - Kinesthetic	33.6 (12.4)	31.2 (12.1)	31.8 (13.0)	0.42	0.45	0.59
KVIQ - Total	72.2 (20.6)	65.8 (22.0)	68.1 (23.3)	0.15	0.25	0.46

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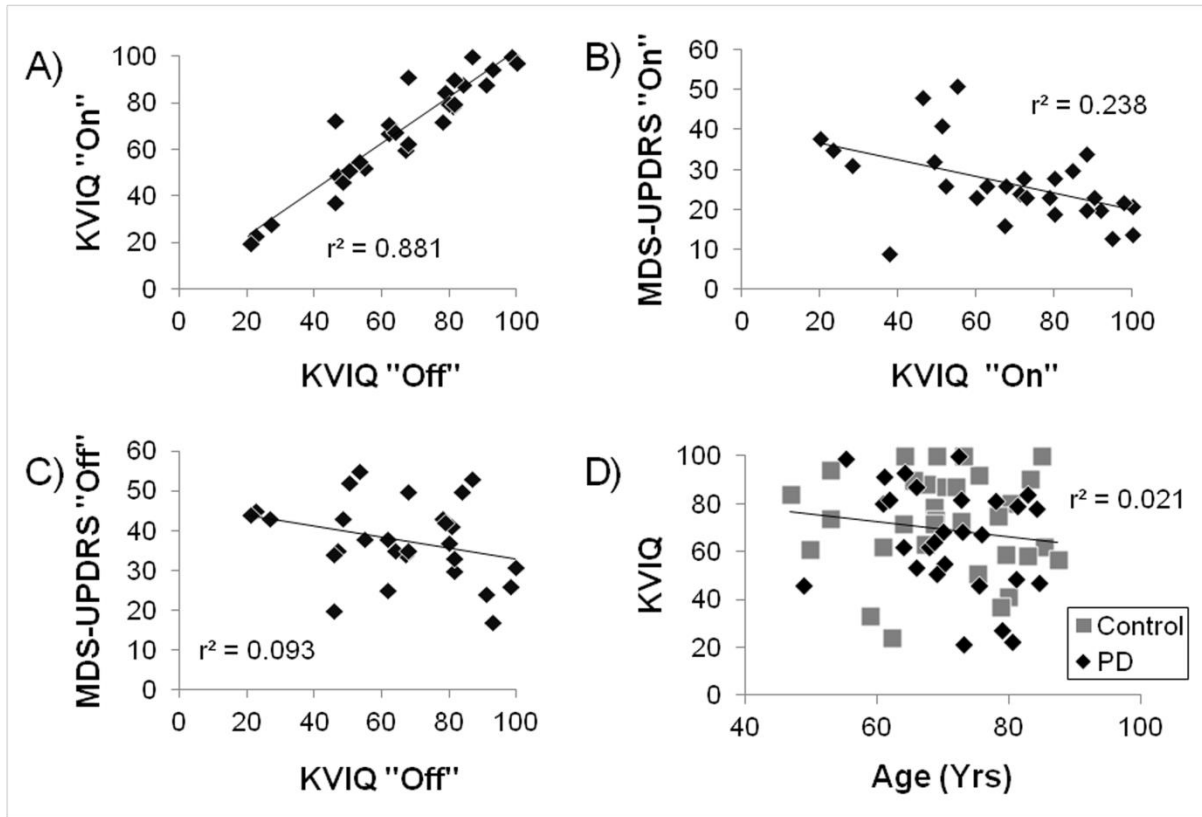
3 Mean (SD). Maximum score of Visual and Kinesthetic sub-components = 50, Maximum
 4 score of KVIQ-Total = 100 (See Methods). PD "Off" = PD "Off" anti-Parkinson
 5 medication, PD "On" = PD "On" anti-Parkinson medication, Control = healthy older
 6 adults. *Paired t-test; #Independent samples t-test

1 Figure 1



2

1 Figure 2



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3

1 **Figure Captions**

2 Figure 1: KVIQ-Unilateral scores for more and less affected side, and dominant and
3 non-dominant side. Maximum score = 70 (See Methods). PD “Off” = PD “Off” anti-
4 Parkinson medication, PD “On” = PD “On” anti-Parkinson medication, Control = healthy
5 older adults.

6

7 Figure 2: Relationships between: (A) KVIQ “Off” and “On” anti-Parkinson medication,
8 (B) Disease severity (MDS-UPDRS III) and KVIQ “On” anti-Parkinson medication, (C)
9 Disease severity and KVIQ “Off” anti-Parkinson medication, and (D) Age and KVIQ
10 (Regression line and r^2 value represents data from all participants; PD data shown is
11 “Off” anti-Parkinson medication).