Table 1
Clinical Investigations of the IGT Used in PD Patients on DRT Except One De Novo Study (Poletti et al.)

Reference	Study Design	Group Description	Years of PD Diagnosis (mean +/– SD)	Hoehn & Yahr (mean +/– SD)	IGT Total Scores
Biars et al. [60]	Case control	PD+ICD ($n=24$)	13.2 +/– 7.1	not reported	No significant group differences
		PD ($n=24$)	11.9 +/– 7.1		
Evens et al. [63]	Case Control	PD-w/DBS ($n=33$)	7.37 +/– 4.26	2.39 +/– 0.59	Significant differences between both PD DBS groups vs. HC; no PD group differences
		PD- nonDBS ($n=33$)	15.27 +/– 5.37	3.17 +/– 0.51	
		HC ($n=34$)	n/a		
Poletti et al. [64]	Case control	PD-de novo ($n=30$)	not reported	not reported	No significant group differences
		HC ($n=25$)			
Gescheidt et al. [65]	Case control	PD-ON ($n=18$)	6.33 +/– 2.87	1.97 +/–0.55	No significant group differences
		HC ($n=18$)			
Gescheidt et al. [66]	Case control	PD-ON ($n=19$)	11.32 +/– 6.42	1.68 +/– 0.58	PD had lower scores, but statistics inconclusive
		HC ($n=20$)			
Czernecki et al. [67]	Crossover ON/OFF	PD-ON/OFF ($n=23$) HC ($n=28$)	14.9 +/– 1.2	ON–2.2 +/– 0.1 OFF–3.8 +/– 0.1	No significant group differences in 1st IGT test. Significant differences in 2nd IGT test
Mimura et al. [68]	Case control	PD-ON ($n=18$) HC ($n=20$)	not reported	Stage 2 –3	No significant group differences
Euteneur et al. [69]	Case control	PD-ON ($n=21$) HC ($n=23$)	7.1 +/– 6.1	Stage 1–3	No significant group differences
Castrioto et al. [70]	Crossover, ON/OFF/DBS	PD-ON/OFF/DBS ($n=20$)	10.3 +/– 3.8	not reported	PD in pre-DBS OFF state had significantly lower scores than HC
		HC ($n=24$)			
Delazer et al. [71]	Case control	PD-ON ($n=10$)	5.25 +/– 6.38	1.8 +/– 0.6	PD and PDD groups performed similarly. Both had significantly lower IGT scores than HC.
		PDD-ON ($n=10$)	8 +/– 4.83	2.5 +/– 0.6	
		HC ($n=20$)			
Kobayakawa et al. [72]	Case control	PD-ON ($n=20$) HC ($n=37$)	6.3 +/– 3.4	1.9 +/– 0.6	PD group had significantly lower IGT scores in last half but not first half
Kobayakawa et al. [73]	Case control	PD-ON ($n=14$)	5.6 +/– 2.7	1.4 +/– 0.6	PD group had significantly lower scores than HC
		HC ($n=32$)			
Kobayakawa et al. [74]	Case control	PD-ON ($n=34$) HC ($n=22$)	6.4 +/– 3.4	1.52 +/– 0.75	PD group had significantly lower scores than HC
Ibarrexte-Bilboa et al. [75]	Case control	PD-ON ($n=24$)	3.06 +/– 1.6	1.73 +/– 0.4	PD group had significantly lower scores than HC
		HC ($n=24$)			
Pagonabarraga et al. [76]	Case control	PD-ON ($n=35$)	8.4 +/– 5	2.2 +/– 0.6	PD group had significantly lower scores than HC
		HC ($n=31$)			
Mapelli et al. [77]	Case control	PD-ON ($n=15$)	4.8 +/– 3.4	not reported	PD group had significantly lower scores than HC
		HC ($n=15$)			
Xi et al. [78]	Case control	PD-ON ($n=15$)	4.33 +/– 5.05	1.97 +/– 0.67	PD group had significantly lower scores than HC
		HC ($n=15$)			

PD, Parkinson's disease; HC, Healthy Control; PDD, Parkinson's disease with dementia; ICD, impulse control disorder; DRT+, dopamine replacement therapy+concomittant meds; DBS, deep brain stimulation.

The neurobiological evidence suggests that decreased cognitive flexibility and increased disinhibition are the most likely contributors promoting decisions to self-discontinue prescribed medications as a function of catecholamine imbalances and neuronal loss in key brain areas associated with EF. To illustrate, Fig. 1, shows the how the progressive neuropathology in PD may decrease response inhibition leading to cognitive inflexibility and non-strategic decision-making. Studies specifically designed to investigate therapeutic compliance and IGT performance among PD patients in the ON vs. OFF states vs. healthy controls in combination with samples of peripheral catecholamine biomarkers would arguably provide a clearer picture of the relationship between decisional capacity, catecholamine function, and therapeutic compliance. As it stands now, it is impossible to infer the potential for therapeutic compliance or non-compliance with the available data from these clinical trials. The findings that patients ON DRT still results in worse performance on the IGT compared to healthy controls indicate two possibilities: 1) that DA deficiencies in cortical regions may be too severe to be replenished to extent to improve strategic-decision making, or 2) deficient NE signaling in PD may be a stronger driving mechanism of impaired decision-making than previously realized.

Thus, it is important to re-examine Fig. 1 and the preclinical and translational data in relation to imaging studies in PD patients undergoing the IGT. Particularly, Kobayakawa et al. (2017) [72] captured brain region activation during the IGT in PD patients in comparison to healthy controls and found lateral and medial orbitofrontal atrophy that significantly correlated with non-strategic decision-making in the PD group. Moreover, imaging research has shown reduced volume, function, and activation in these brain areas are associated with disinhibition which may suggest the use of the IGT to identify problematic and disadvantageous decision-making in PD populations [65, 72, 79].

As previously discussed, both DA and NE work hand-in-hand towards regulating reward-perception, response inhibition, and cognitive flexibility in particular brain areas that are associated with increased spontaneity and careless decision-making. These characteristics have strong potential to influence medication non-compliance. To this point, baseline IGT net total scores have been shown to predict future substance relapse in non-PD populations [24, 80–81]. Importantly, Stevens et al. (2014) [82] found that the IGT predicted patients who dropped out of treatment prematurely. Both Nejtek et al. (2013) [24] and Stevens et al. (2014) [82] found that patients who either relapsed or dropped out of treatment were unable to learn to inhibit disadvantageous decisions on the IGT, even after multiple test administrations at different time points.

Given the evidence that a single assessment using the IGT can predict relapse and treatment compliance in other patient populations, this test may have potential to identify individuals who might be prone to spontaneously self-discontinue their medications. We argue more controlled studies that evaluate IGT performance in the ON and OFF states will help strengthen the premise that a certain deficiency in cortical catecholamine levels may predict the likelihood of therapeutic non-compliance in the PD patient. Thus, more work is also warranted to examine cognitive characteristics in preclinical, prodromal PD, and PD patients to identify those who may be at-risk for therapeutic non-compliance. The little available clinical data examining the use of the IGT in PD populations provides a glimpse of its possible utility. Prospective studies that control for disease duration, disease severity, and DRT therapy levels, and possibly include cortical catecholamine image analysis would go a long way to help advance our knowledge to ascertain decision-making correlates medication response and compliance.

DO MEN AND WOMEN WITH PD PERFORM THE IGT DIFFERENTLY?

The prevalence and incidence of PD is approximately two-fold higher in men than women with women diagnosed at older ages than men [83–86]. In the early stages of PD, sex differences in PD motor symptom phenotype include men more often presenting with bradykinesia while tremors and postural instability are generally observed in women [86–88]. While sex differences in PD motor symptomatology are known, the influence of sex on executive functioning is understudied. However, since the seminal work of Maccoby and Jacklin [89], it is well-documented in healthy populations across the lifespan that females have better verbal memory, faster psychomotor and processing speed than males; and males have better visuospatial memory, spatial recognition, and mental rotation than females [90–92]. The same EF differences hold true for women and men with PD. The available data suggests that women with PD have better verbal memory

[86], executive and global cognitive functioning than men [93–98]. Conversely, men with PD have better visuospatial memory than women [93, 99–103]. Data suggest that women learn verbal lists faster, have more efficient frontostriatal DA regulation, and higher DA receptor expression in the striatum that may be associated with higher estrogen levels [86, 104]. The intersection of catecholamines and estrogen in PD patients presents an interesting perspective in possibly explaining the sex differences in decision-making in the PD population [100, 104–109].

Although non-strategic decision-making is more common in men with PD than in women [11, 109–112], both sexes may exhibit risk-taking behaviors (e.g., pathological gambling, compulsive buying, etc.) while temporal discounting (e.g., inability to delay gratification) is more associated with men than women [6, 11, 109–111, 113]. In PD populations, although both sexes may exhibit some non-strategic decision-making [77, 78, 113], there remains a need to determine the extent to which this cognitive domain influences clinical outcomes in men compared to women. The general consensus in healthy adult populations performing the IGT is that men learn the strategy of choosing advantageous cards quicker than women, but over time women catch up to the strategy and the end net result is the same for both sexes [114–116]. Thus, performance on the IGT in the PD population may not be uniquely reflective of PD as overall sex differences in cognitive functioning exists even in healthy controls.

To our knowledge, there are no studies specifically examining sex differences in IGT performance in patients with PD in relation to advancing a clinical perspective for sex-specific therapeutic compliance. In contrast, some data suggests that women with PD may have latent complications associated with DA therapy [116] that may influence careless decision-making. However, it is currently not possible to determine the clinical applicability of IGT performance in relation to predicting the apparent sex differences found in PD. Although men with PD may have a higher risk for making non-strategic decisions than women, it is unclear whether or not this translates into men having more problems with therapeutic compliance and disease resiliency.

INTEGRATING THE FINDINGS

It is evident that many PD patients will have decision-making problems during the course of their illness. Non-strategic decision-making may be applied to therapeutic complications associated with medication non-compliance leading to poor health trajectories overall. As there are emerging reliable physiological, image-based, and genetic biomarkers associated with predicting risks for prodromal and early stage PD [117, 118], the IGT may be a useful companion to detect non-strategic decision-making already on-board prior to motor impairment. Of the phenotypic markers related to prodromal PD, the most well-documented and conclusive markers of prodromal PD is REM sleep behavior disorder (RBD) [117, 118]. Given the emphasis on RBD as a predictive marker of prodromal PD, we found one study that that described IGT outcomes in RBD patients that might provide a rationale for examining the IGT's applicability in PD.

In a non-PD sample, Delazer et al. (2012) [119] used a neuropsychological battery measuring various domains of EF in RBD patients compared to healthy age- and education-matched controls to exclude cognitive impairment in their sample. The researchers then used the IGT to specifically measure non-strategic decision-making, the Information Sampling Task, Intra/Extra Dimensional Shift task, One Touch Stockings of Cambridge (similar to Tower of London), and the Go-NoGo Task to measure cognitive impulsivity and complex problem solving. The outcomes of this study showed that only the IGT revealed significant group differences in RBD compared to age-matched controls, as RBD patients made significantly more non-strategic, disadvantageous decisions. This study indicates that the IGT may identify subtle cognitive problems by interrogating strategy-based decisional capacity in PD patients that might not otherwise be revealed with other types of neuropsychological tests specifically designed to diagnose cognitive impairment. For example, many of the neuropsychological tests require adequately intact motor functioning (e.g., Trail-making Tests A and B, Rey Osterrieth Complex Figure Test, Block design, Bells Test, etc.) while others depend on visual color accuracy (e.g., Wisconsin Card Sorting Task, Stroop Color Word Test, etc.). As a computerized test that does not depend on visuospatial capabilities nor color accuracy, the IGT may be a viable alternative assessment tool especially when decision-making is of particular interest.

The most recent and interesting data elucidating decisional capacity in PD suggests that there is significant loss of noradrenergic functions from the LC and DA loss from the SN impacting its connection to

the PFC. This new finding of the SN-PFC connection expands the traditional view of the roles DA and VTA alone may have played in EF and decision-making in PD populations. Now, accumulating evidence is pointing towards a combined contribution of LC and NE *with* nigrostriatal and mesolimbic DA signaling in the OFC and PFC that are critically important neural factors underlying cognitive flexibility and response inhibition necessary for strategic decision-making.

The significant relationships among cognitive and motor functioning, therapeutic compliance, and disease resilience present a clinically challenging rationale for using the IGT to assess decision-making prior to global cognitive or motor decline. However, in the absence of frank cognitive and motor impairment, the IGT may have the potential to evaluate an individual's capacity to make strategic decisions prior to a firm PD diagnosis. Particularly relevant to PD patients is the high mortality rate associated with therapeutic non-compliance with complex DA treatment regimens that depends on a patients' ability to make strategic decisions while inhibiting impulses to self-discontinue or adjust their medication regimen. Although more research is needed, when all other domains of cognitive functioning are intact, the IGT may help identify subtle, non-strategic decision-making in those at-risk for preclinical or prodromal PD and therapeutic non-compliance.

CONCLUSION

Evidence of impairments to catecholamine function can be interrogated at multiple levels, including CNS-imaging and serum analysis. These biomarkers, if seen in conjunction with subtle cognitive impairments seen in premotor and early-stage PD or with other indicators of compromised peripheral functions such as dysautomnia [120], would increase the likelihood of detecting PD pathology or identify the clinical issue facing the PD patient, which as we discussed, include therapeutic non-compliance. As such, the IGT is argued to be a useful companion in this regard.

This review presents the currently available data from animal models and human studies investigating the neurobiology of EF in PD and the applicability of the IGT to reveal decisional capacity associated with the neural areas, pathways, and/or catecholamine dysfunction underlying PD neuropathology. Using the IGT to identify potential problems with therapeutic compliance due to the high rate of mortality in PD resulting from decisions to self-discontinue or self-adjust DRT is worthy of future research. We also found that the available data indicates that the IGT interrogates the same neural areas involved in PD neuropathology. Here, we have summarized the available data that may point researchers toward a more unified approach concerning the applicability of using the IGT in PD, towards identifying risks for preclinical or prodromal PD (if used alongside other well-established markers), and therapeutic non-compliance. However, the IGT may not differentiate or predict decisional capacity in men versus women with PD.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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