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Multimedia Aided Consent for Alzheimer's Disease Research

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ABSTRACT

Objectives: Optimizing the research consent process simultaneously fosters respect for autonomy and protection of those with diminished capacity for autonomy. This study evaluated the effectiveness of an enhanced research consent procedure, employing multimedia disclosure and corrective feedback, in improving decisional capacity among 114 people with mild-to-moderate Alzheimer's disease (AD) and 134 non-psychiatric comparison (NC) subjects.

Methods: Participants were randomized to consent type (routine versus enhanced) and protocol type (lower versus higher risk). Outcomes included a 5-item questionnaire assessing immediate comprehension, MacArthur Competence Assessment Tool for Clinical Research assessing four components of decision-making capacity, and categorical decisional capacity (based on a cut-score established in reference to expert judgments for a subset of participants).

Results: There was no significant effect of the enhanced consent procedure, relative to routine consent, on immediate comprehension or decisional capacity.

Conclusions: Multimedia tools do not appear to be the solution to better consent for AD research.

Clinical Implications: Given the ethical primacy of informed consent and issues of justice for impaired populations who might be harmed by an absence of research-based treatment advances, continued search for ways to more meaningfully engage people with AD in the consent or assent process is warranted.

KEYWORDS

Autonomy; competence; ethics; dementia; informed consent

Introduction

Alzheimer's disease (AD) extracts an enormous emotional and financial toll. Advances in prevention and treatment require ongoing research, in turn requiring enrollment of participants with AD. While ethical and humanitarian considerations compel society to foster prevention and treatment of AD, there is an equally compelling need to protect vulnerable individuals participating in research with uncertain individual benefit (Dunn & Alici, 2013; Howe, 2012; Kim, Appelbaum, Jeste, & Olin, 2004). As stated in the Belmont Report, the principle of respect for persons incorporates "two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Among patients with AD, some clearly require such protections, when their capacity to make autonomous research decisions is impaired. However, some patients with AD retain decision-making capacity and autonomy for research decision-making (Karlawish et al., 2008; Palmer et al., 2013). Efforts to optimize the consent process, in order to maximize each individual's ability to make informed decisions, may simultaneously foster both autonomy and protection.

Studies from other patient populations may give some insights into viable means of improving the consent process for AD. Schizophrenia, like AD (Karlawish, Casarett, & James, 2002; Kim & Caine, 2002; Marson & Harrell, 1999; Palmer et al., 2005, 2017), is a risk factor for impaired decisional capacity (Appelbaum, 2006; Dunn, Candilis, & Roberts, 2006; Jeste, Depp, & Palmer, 2006). Also, the cognitive

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deficits of schizophrenia, rather than the primary psychotic symptoms, are the strongest predictors of capacity to consent (Palmer & Savla, 2007). Yet, the level of manifest decisional capacity among people with schizophrenia, and the proportion of people thereby deemed to have impaired capacity, is affected not only by the complexity of the information, but also by the quality of the consent process (Dunn, Palmer, & Karlawish, 2007). Simple procedural changes to routine consent, including provision of corrective feedback, have been shown to improve at least some participants' understanding of disclosed information in schizophrenia research consent processes (Dunn, 2006; Palmer, Cassidy, Dunn, Spira, & Sheikh, 2008). Further benefit and improvement in the consent process may be achievable through the use of multimedia learning tools.

We previously found that people with schizophrenia randomly assigned to a DVD-based multimedia-aided consent process had significantly better understanding of disclosed information, and were more likely to be deemed "capable" to consent, relative to those receiving a routine consent procedure (Jeste et al., 2009). The cognitive deficits associated with AD versus schizophrenia are not equivalent in typical level/severity, pattern, or course (Palmer, Dawes, & Heaton, 2009; Weintraub, Wicklund, & Salmon, 2012). One key difference is that although rapid forgetting is a hallmark of AD (Tröster et al., 1993), people with schizophrenia generally have adequate retention of information, once learned (Heaton et al., 1994). However, cognitive deficits commonly associated with both disorders include difficulties with learning/acquisition of new information, as well as executive functions, both of which have clear relevance to decisional capacity (Palmer & Harmell, 2016).

Our original DVD-based consent process was grounded in multimedia learning principles. The term multimedia refers to presentation of information via both verbal and visual channels, which in learning research has been shown to facilitate acquisition of information and comprehension (Mayer, 2001, 2008). By simultaneously combining presentation of information in the auditory and visual-spatial channels of working memory (Baddeley, 2007), and visually displaying information and relationships that tend to be implicit or require lengthy description when presented verbally (Anglin, Vaez, & Cunningham, 2004; Larkin & Simon, 1987; Wallace, West, Ware, & Dansereau, 1998), multimedia tools may help reduce the cognitive load with processing such information, and may thereby compensate for information processing deficits associated with schizophrenia or AD. However, there has been minimal research to empirically evaluate the efficacy of multimedia aids for consent among people with AD.

In a systematic review of the efficacy of multimedia aids for the research consent process (Palmer, Lanouette, & Jeste, 2012), we found that only 1 of 20 studies identified was focused on AD patients (Mittal et al., 2007). That study yielded equivocal results due to a small sample size and lack of a routine consent comparison procedure. Specifically, in a combined sample of 19 people with mild-to-moderate AD and 16 with mild cognitive impairment (MCI), Mittal and colleaagues (2007) compared the effectiveness of a PowerPoint aided consent process, providing simultaneous visual-pictorial and verbal-textual information versus an enhanced written consent form, with key components provided in bold font. None of the comparisons of understanding, reasoning, or appreciation differed among the two consent groups, although there was a small to medium effect size difference, Cohen's d = .29, favoring the PowerPoint aided consent group, for initial post-consent understanding of disclosed information.

The goals of the present study were to evaluate the efficacy of a multimedia aided enhanced consent process incorporating corrective feedback, compared with routine consent, among individuals with mild-to-moderate AD and non- neuropsychiatric comparison (NC) subjects. As comprehension of consent information may be affected by the complexity and risks of a specific protocol (Palmer et al., 2013), we examined the effects of enhanced versus routine consent among people with AD and NCs in reference to two hypothetical (yet realistic) protocols: (a) a Phase 3 cholinomimetic drug trial ("lower risk") and (b) a Phase 2 immunotherapy trial ("higher risk"). We hypothesized that: 1) compared with routine consent, enhanced consent would yield superior understanding, appreciation, and reasoning among all participants; and 2) enhanced consent would have a stronger effect among individuals with AD relative to NCs, and among those presented

with the higher risk trial compared with those presented with the lower risk trial.

Methods

Participants

Participants were 114 people with possible or probable Alzheimer's disease (AD) of mild-to-moderate severity (for the present study defined as an MMSE total ≥ 15), and 134 non-neuropsychiatric comparison (NC) subjects. Participants with AD were recruited through the University of California, San Diego (UC San Diego) Shiley-Marcos Alzheimer's Disease Research Center (ADRC), AD caregiver support groups, UC San Diego Geriatric Psychiatry Research Center, physician referrals, and memory care centers. NC subjects were recruited through the Stein Institute for Research on Aging, Geriatric Psychiatry Research Center, ADRC, retirement homes, senior centers, word of mouth, Craigslist, and community flyers.

Inclusion criteria were diagnosis of possible or probable AD (or, for NC subjects, no history of a neuropsychiatric condition potentially affecting cognitive function), MMSE total ≥ 15, age ≥ 50 years, fluency in English, and informed written consent from the participant (or participant assent with consent from legally authorized representative). (There is no single consensus cut-score on the MMSE for defining the mild-to-moderate range of impairment, but the criterion of MMSE total ≥ 15 was intended to approximate the range functioning at which active engagement in the consent process remains potentially viable.) Exclusion criteria were other neurologic conditions potentially affecting cognition or physical/medical conditions interfering with completion of the study procedures. (There were no exclusion criteria based on treatment status.) A subset of participants provided data to a prior report on predictors of decisional capacity (Palmer et al., 2017), however, this is our first examination of the utility of the enhanced consent procedure. This study was approved by the UC San Diego Human Research Protections Program. (Because of the minimal risk nature of this study, a lower level of comprehension ability was needed for consent than for a more complex or greater than minimal risk randomized clinical trial (Saks, Dunn, & Palmer, 2006).)

Diagnosis of possible or probable AD was generally pre-established by the recruitment site. Sixty-six of the 114 (57.9%) participants with AD were recruited through the ADRC where diagnosis involved confirmation by two independent neurologists who reviewed relevant clinical, neurologic, and neuropsychological information. For the other participants, diagnosis was generally established by their treating clinician or another neurologist. Absence of neuropsychiatric disorders among NCs was established with the Mini International Neuropsychiatric Interview (Sheehan, Lecrubier, & Sheehan, 1998).

Measures and procedures

Sociodemographic information

Age, education, gender, and ethnicity were determined via interview or record review.

Cognitive impairment

Severity of cognitive impairment was evaluated with the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and Mattis Dementia Rating Scale – Second Edition (DRS-II; Jurica, Leitten, & Mattis, 1991) total scores.

Hypothetical protocols

Subjects were randomly assigned to the consent process for either of two clinical trials: (a) a Phase 3 trial of an investigational cholinomimetic drug (lower risk protocol), or (b) a Phase 2 trial of an AD (anti-amyloid) immunotherapy (higher risk protocol). These trials were selected to foster ecological validity and to permit comparison of two protocols with varied information about risks and benefits. Four of the five currently FDA-approved medications for AD are cholinesterase inhibitors, and all five are symptom management focused rather than disease modifying. Thus, we designed the Phase 3 trial as a prototypic "me-too" drug study, with the likely risks being unpleasant but not disabling or irreversible. In contrast, immunotherapy and other disease modifying intervention trials are growing in prevalence, yet currently tend to be in earlier phases (Phase 1 or Phase 2), and thus have less certain or well-established risk:benefit (safety/efficacy) profiles (Cummings, Morstorf, & Zhong, 2014; Lemere, 2013); some of the early immunotherapy trials included incidents of

participant death. Thus, some of the risks for the Phase 2 trial were described as less well established, but including possible severe/irreversible risks, even if unlikely. Further details of these protocols are available in Palmer et al. (2017).

Simulated consent procedures

Participants were randomly assigned to review the assigned protocol using routine or enhanced consent procedures.

Routine consent

For routine consent, a trained research assistant (RA) explained that she would read and discuss the consent form with the participant. The RA encouraged the participant to read along and to stop the RA at any point where anything was unclear or when the participant had any questions. The RA paused after each major conceptual unit, such as after the first paragraph regarding study purpose, and asked the participant if she or he had any questions about that information. The RA answered any questions, and then proceeded to review the remainder of the consent form with the participant in the same manner.

Enhanced consent

The enhanced consent procedure expanded on routine consent by adding a more structured, iterative process and by incorporating multimedia tools into the consent presentation. The RA sat next to the participant in front of a laptop computer with the screen facing the participant and explained that they would be discussing the information contained in the printed consent form, and that this discussion would include viewing a series of video clips describing and demonstrating important information from the consent form. For instance, the participant was shown a short video explaining the study purpose, and was then asked to describe that information in his or her own words. The participant's response was scored by the RA as 0 (incorrect), 1 (partially correct), or 2 (correct). If the response was scored 0 or 1, the RA re-explained the information, and/or replayed the video segment, as appropriate to the nature and level of the misunderstanding. After any re-presentation the RA again asked the participant to explain that information in his or her own words. Once the participant provided a correct 2-point response, or after three unsuccessful attempts, the RA proceeded to the other major segments of the consent process in the same manner. (Nine NC subjects and 33 participants with AD earned less than 2-points on at least one item by trial 3.)

In conducting and scoring the embedded questions, the RA used five questions pre-identified for the low- and high-risk protocols (the five questions targeted participant understanding of the study purpose, procedures/assessments, risks, benefits, and the voluntary nature of participation) similar to the 5-item questionnaires developed and embedded into the consent process for several (non-simulated) biomedical studies (Palmer et al., 2008). The questionnaires used by the RAs for the present study included specific/concrete scoring guidelines for establishing a score of 0, 1, or 2, based on those published with the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) (Appelbaum & Grisso, 2001). RAs also recorded the participant's responses to each query. After completion of data collection for this study another RA (not involved in data collection), blindly re-scored 95 of the questionnaires; inter-scorer reliability (Intraclass Correlation Coefficient [ICC]) for Trials 1, 2, and 3 totals were ICC > .981.

Central components of multimedia theory include using multimedia to reduce processing of irrelevant information, managing processing required to mentally represent key information, and maximizing generative processing (i.e. that needed to comprehend relevant information) (Mayer, 2008). Grounded in multimedia learning theory, we focused on using multimedia materials only where they could reasonably be expected to facilitate learning. For instance, according to the segmenting principle, learning is facilitated when presentation is paced to the needs of the learner. Thus, instead of providing consent in a single DVD as in our schizophrenia study (Jeste et al., 2009), each conceptual unit was broken up into a short segment available on a menu of options on the laptop, allowing the RA to present (and re-present) specific information with a pacing per each individual's needs. Multimedia principles also guided the content, e.g. purely verbal or

textual descriptions of placebo and randomization can be difficult for laypeople to comprehend. Thus, the enhanced consent materials included an animated representation of two pills cut open, which looked identical except one had small letter *m*'s inside, indicating presence of medication. Randomization was illustrated with an animated sequence showing different color balls being drawn from a hat. Also, multiple calendars with key events highlighted were shown to illustrate the study timeline and key events in a way that could be immediately communicated graphically, but would require more mental processing if described aurally or with printed text alone.

Consent-related assessments

Immediate comprehension

To determine information subjects retained at the point when participants in a clinical trial would generally be asked to sign the consent form, following the simulated consent process, comprehension was immediately assessed and scored by the RA with five questions (identical to those embedded into the enhanced consent process except that no corrective feedback was provided). After data collection another RA blindly rescored 192 of these questionnaires (ICC = .966).

Decision-making capacity

Participants next met with a second RA (RA-2) kept naive to the participant's consent condition. RA-2 assessed the participant's consent capacity with a modified version of the MacCAT-CR (Appelbaum & Grisso, 2001), that provides subscale scores for Understanding (range = 0–26), Appreciation (range = 0–6), Reasoning (range = 0–8), and Expression of a Choice (range = 0–2), with higher scores representing better performance. In the standard MacCAT-CR, the questions are interlaced with the initial disclosure of consent information. However, our goal was to evaluate the effectiveness of an enhanced consent procedure. Therefore, similar to prior enhanced consent studies (Jeste et al., 2009; Mittal et al., 2007; Rubright et al., 2010), we omitted the initial embedded disclosures from the MacCAT-CR interviews. Subjects' understanding score under these conditions was scored as Trial 1. However, in accord with standard MacCAT-CR administration procedures, any misunderstood information was subsequently re-explained and understanding was re-assessed, which was scored as Trial 2. Inter-scorer reliability was fostered through extensive training, including observing and double scoring MacCAT-CR interviews during training, specific scoring criteria and guidelines as indicated in the MacCAT-CR manual, and weekly lab meetings with the first author (BWP) to discuss scoring and other study issues.

Categorical capacity determination

For categorical determinations of capable versus incapable status we used a cut-score of 20.5 on the MacCAT-CR Understanding subscale Trial 2. Details of the identification of this cut-score are available in our prior report (Palmer et al., 2017). Briefly, using methods previously developed by one of the co-authors (SYK) (Kim et al., 2001, 2007, 2011), this cut-score was developed and validated relative to determinations of three geriatric psychiatrists experienced in making capacity determinations. Following further training by SYK, the judges independently viewed videotapes of 40 of the MacCAT-CR interviews from the AD group, and then provided capacity determinations. Final status was based on the majority opinion, but inter-judge reliability was good (ICC = .779).

Statistical analyses

Sociodemographic characteristics, severity of cognitive impairment (DRS-II total), immediate comprehension, and decisional capacity were compared between consent groups within each diagnostic group using one-way analyses of variance (ANOVA) for continuous variables or Pearson's chi-square for categorical variables. For significant omnibus ANOVAs, follow-up pairwise comparisons were conducted with Tukey's least significant difference procedure. Because the Expression of a Choice subscale was significantly skewed (skew/standard error of the skew > 3.00) even after attempting transformations, non-parametric Kruskal-Wallis tests were used to compare performance among consent groups on this variable. We also conducted a post-hoc exploratory analysis within the AD group—i.e., collapsing across protocol types, we compared the proportion of people with AD classified as capable versus

incapable in the routine versus enhanced consent conditions with Pearson's chi-square. Statistical significance was defined as $p < .05$ (two-tailed).

Results

Demographic and cognitive characteristics

Within each diagnostic group, there were no significant differences between consent procedure by protocol type groups in age, education, gender, ethnicity (% Non-Latino Caucasian), or cognitive impairment (Table 1).

Effects of protocol type and consent method

Among NC subjects, there was a significant difference on the MacCAT-CR Appreciation score (Table 2). Follow-up pairwise comparisons indicated that the mean Appreciation score of those in the higher risk/enhanced consent condition was significantly lower than that of subjects in the lower risk/routine condition and the lower risk/enhanced condition. Within each diagnostic group, there were no other significant differences among the four protocol types by consent method conditions in terms of demographic characteristics, cognitive impairment, immediate comprehension, or decision-making

Table 1. Demographic and cognitive characteristics.

	Lower Risk		Higher Risk			
	Routine	Enhanced	Routine	Enhanced	Statistical Test with *df*	*p*-Value
Normal comparison subjects	n = 35	n = 34	n = 35	n = 30		
Age	79.0 (9.7)	77.7 (9.8)	77.7 (9.4)	79.2 (9.4)	F(3, 130) = .25	.859
Education	14.0 (2.6)	14.0 (2.2)	14.7 (2.8)	14.9 (2.6)	F(3,130) = 1.15	.332
Gender (% Women)	51.4%	50.0%	65.7%	50.0%	$\chi^2(3) = 2.43$	.488
Ethnicity (% Non-Latino Caucasian)	88.6%	88.2%	82.9%	76.7%	$\chi^2(3) = 2.26$	.520
MMSE Total	27.5 (2.2)	28.1 (2.0)	28.0 (1.9)	27.9 (1.8)	F(3, 130) = .80	.498
DRS-II Total	133.3 (7.6)	134.1 (6.5)	134.9 (8.2)	134.2 (7.7)	F(3, 129) = .28	.836
Alzheimer's disease	n = 33	n = 26	n = 31	n = 24		
Age	79.7 (6.5)	79.4 (6.7)	79.2 (7.3)	79.8 (7.3)	F(3,110) = .05	.987
Education	13.5 (2.6)	14.4 (2.8)	14.3 (3.6)	15.3 (2.7)	F(3,108) = 1.67	.177
Gender (% Women)	39.4%	61.5%	38.7%	41.7%	$\chi^2(3) = 3.90$	.273
Ethnicity (% Non-Latino Caucasian)	81.8%	88.0%	80.6%	91.7%	$\chi^2(3) = 1.73$	.630
MMSE	21.0 (3.2)	20.9 (3.9)	22.5 (3.4)	21.7 (3.8)	F(3,109) = 1.24	.299
DRS-II Total	110.3 (13.6)	112.9 (13.6)	117.8 (11.8)	110.1 (17.6)	F(3,103) = 1.87	.140

Note: MMSE = Mini Mental State Examination; DRS = Mattis Dementia Rating Scale - Second Edition.

Table 2. Effects of protocol type and consent method.

	Lower Risk		Higher Risk			
	Routine	Enhanced	Routine	Enhanced	Statistical Test with *df*	*p*-Value
Normal comparison subjects	n = 35	n = 34	n = 35	n = 30		
5-item total	9.0 (1.3)	9.5 (.9)	9.2 (1.4)	9.7 (.6)	F(3, 129) = 2.22	.090
MacCAT-CR						
Understanding Trial 1	22.6 (2.6)	22.4 (3.0)	22.7 (4.0)	21.3 (4.0)	F(3,130) = 1.05	.374
Understanding Trial 2	25.3 (1.1)	25.2 (1.1)	24.9 (2.3)	24.8 (2.2)	F(3,130) = .21	.890
Appreciation	5.2 (1.0)	5.5 (.8)	5.1 (1.1)	4.7 (1.1)	F(3,128) = 4.10	.008[a]
Reasoning	7.3 (1.3)	7.6 (.7)	7.5 (.9)	7.5 (.8)	F(3,129) = .86	.463
Expression of a Choice	1.9 (.2)	1.9 (.2)	1.9 (.3)	2.0 (.0)	$\chi^2(3) = 1.97$	.579
Capable (% Yes)	100.0%	100.0%	91.4%	96.7%	$\chi^2(3) = 5.91$	.116
Alzheimer's disease	n = 33	n = 26	n = 31	n = 24		
5-item total	5.4 (2.6)	6.0 (2.1)	5.9 (2.6)	6.0 (3.0)	F(3,108) = .44	.726
MacCAT-CR						
Understanding Trial 1	11.5 (6.1)	12.8 (6.3)	11.9 (7.8)	14.0 (7.0)	F(3,110) = .69	.560
Understanding Trial 2	15.1 (6.9)	17.8 (7.0)	15.7 (7.7)	16.8 (7.6)	F(3,110) = .75	.523
Appreciation	4.2 (1.3)	4.2 (1.8)	4.1 (1.7)	4.2 (1.6)	F(3,110) = .03	.994
Reasoning	5.6 (2.5)	6.9 (1.5)	6.3 (2.4)	6.2 (2.5)	F(3,108) = 1.54	.208
Expression of a Choice	1.7 (.6)	1.8 (.6)	1.5 (.8)	1.7 (.7)	$\chi^2(3) = 2.11$	.550
Capable (% Yes)	30.3%	46.2%	32.3%	45.8%	$\chi^2(3) = 2.63$	.453

[a]Higher Risk Enhanced Consent < Lower Risk Routine Consent and Lower Risk Enhanced Consent.
Note: MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research.

capacity (MacCAT-CR subscale scores and percent categorized as capable to consent).

Among people with AD, approximately 46% of participants in the enhanced consent condition were categorized as capable in each of the protocol types, compared with 30% to 32% within the routine consent groups. We conducted a post-hoc exploratory analysis combining subjects from the two protocol types, but found no significant differences in the proportion of people with AD categorized as decisionally capable in the routine (31.3%) versus enhanced (46.0%) groups (X^2[1, N = 114] = 2.60, p = .107).

Discussion

Efforts to more effectively engage people with AD in the process of informed consent for research are vital, not only to the ethical foundation of research, but also to the mission of advancing research to prevent and treat AD. Based on earlier positive results from studies of enhanced consent procedures for people with schizophrenia (Dunn et al., 2002; Jeste et al., 2009; Moser et al., 2006; Wirshing, Sergi, & Mintz, 2005), and grounded in principles of multimedia learning (Mayer, 2001, 2008), we hypothesized that an enhanced consent procedure involving corrective feedback and multimedia learning tools would result in better decisional capacity, assessed in three different ways, among people with mild-to-moderate AD. However, regardless of whether randomized to the lower or higher risk protocol type, participants who received the enhanced consent procedure did not demonstrate significantly better decisional capacity scores compared with those who received the routine consent procedure.

The one exception to the otherwise statistically non-significant findings was that NCs reviewing the higher risk protocol via the enhanced consent procedure evidenced significantly lower appreciation than the NC subjects in either consent procedure condition reviewing the lower risk protocol. Although statistically significant, we are reluctant to reject the null hypothesis or overly interpret this one isolated finding. There is no clear conceptual model or reason to anticipate a differential effect of the protocol type on appreciation, but not on understanding, nor any reason to expect such a specific effect only among NC subjects. The conceptualization and operationalization/measurement of the appreciation subcomponent of decisional capacity may also be problematic relative to the other three components (Moye, Azar, Karel, & Gurrera, 2004; Moye, Karel, Azar, & Gurrera, 2004). Together with the possibility of inflated type 1 error from multiple comparisons, these considerations suggest interpretive caution is warranted in regard to the isolated appreciation finding, pending independent replication.

The absence of significant benefits from multimedia consent among AD patients contrasts with the modest, but statistically significant, benefits from DVD-aided research consent for people with schizophrenia (Jeste et al., 2009). It is possible that differences in the nature of cognitive deficits associated with schizophrenia versus AD may moderate the effectiveness of enhanced consent procedures. Although people with schizophrenia often have deficits in initial acquisition of information, even when other cognitive domains are relatively spared (Palmer et al., 1997), one generally intact cognitive dimension is information retention (Brazo, Ilongo, & Dollfus, 2013; Heaton et al., 1994; Paulsen et al., 1995). In contrast, rapid forgetting is the hallmark of AD, even in its earliest clinical manifestations (Bondi et al., 2008; Mansoor et al., 2015; Salmon & Bondi, 1999; Tröster et al., 1993). People with schizophrenia may benefit from multimedia consent methods because such methods help to circumvent the deficits in acquisition of new information. In contrast, people with even mild to moderate AD may forget any new information as soon as it leaves working memory (a matter of seconds as attention focuses on other information). Improved means of teaching consent relevant information to people with AD may be doomed to failure due to this rapid forgetting.

It may still be possible to structure consent procedures so that patients would not have to remember the information, yet could still meaningfully engage in the consent—or at least assent—process. Rubright and colleagues (2010) showed that providing AD participants with a one-page printed memory/organizational sheet, saliently summarizing key information, may foster manifest decisional capacity if participants are permitted to use the memory sheet not only during initial disclosure, but also during subsequent assessment of comprehension/decisional capacity. Relative to those receiving routine consent,

significantly more of their AD participants receiving this aid were deemed capable of providing informed consent (18% versus 48%). Note, however, that even in the memory aid condition, slightly more than half of their participants were deemed not capable of consent. Thus, there remains an unmet need to address further how to meaningfully engage people with mild-to-moderate AD in the research consent or assent process.

Beyond the development of standard symptom management compounds, over the past decade there has been increasing interest in disease-modifying therapies (Sugino et al., 2015). As the goal of such efforts is to arrest the neuropathological cascade that leads to clinical dementia, the participants in such trials tend to be those with MCI or otherwise deemed "at risk." As participants in the pre-clinical stages are likely to have less cognitive impairment, their risk of impaired decisional capacity may be lower. On the other hand, there is evidence that MCI may be a risk factor for worse decision making (Han, Boyle, James, Yu, & Bennett, 2015; Jefferson et al., 2012, 2008; Okonkwo et al., 2007). Moreover, the bar for capacity for early intervention trials may need to be higher due the complexity of risks and uncertainty of benefits. Thus, even with a shift toward disease modifying trials, the need to find effective means of obtaining genuinely informed consent remains paramount.

One potential limitation of the present study is that the use of hypothetical research scenarios may have diminished participants' interest in or motivation to attend to the consent material. However, this method enabled us to examine systematically the effects of the enhanced consent procedure in a larger sample than would have been available in most specific clinical trials, as well as allowed us to experimentally control both consent procedures and protocol type, thereby maximizing power to detect a meaningful effect size, had it been present. Even if attention were improved in the context of recruitment for an actual clinical trial, it appears unlikely those attentional influences would be strong enough to result in a substantially larger effect size for the enhanced consent procedures. It is also possible that our results would not generalize to other decisions or protocols markedly different from those employed in the present study. However, the two protocols were distinct, thus representing an internal replication, and were designed to be ecologically valid, in that cholinomimetic and amyloid clearance compounds currently represent common avenues of AD clinical research (Cummings et al., 2014; Ferreira-Vieira, Guimaraes, Silva, & Ribeiro, 2016).

Despite the above limitations, it appears unlikely that enhanced consent procedures, such as those used in our study, will markedly improve comprehension of informed consent disclosures for people with AD. This finding adds to the general skepticism about the value of multimedia research consent expressed in some prior reviews of the broader (non-AD) literature (Flory & Emanuel, 2004; Synnot, Ryan, Prictor, Fetherstonhaugh, & Parker, 2014). However, given the centrality of rapid forgetting in AD, we believe it would be premature to conclude that multimedia tools (if properly designed and tested) have no benefit for patients with non-memory focused disorders.

The largely negative findings leave the question of what to do about the quandary of the need for clinical research in AD in light of the risk for impaired decision making capacity among some, albeit not all, persons with AD. Relevant to this issue, Peisah, Sorinmade, Mitchell, and Hertogh (2013) suggested a more inclusionary approach to consent than provided in the standard capable/incapable framework. Rather than viewing the purpose of capacity assessments as a means to categorically determine decisional capacity, they argued for evaluating the kinds of support people with "decision-making disabilities" require to be meaningfully involved in decision-making. NC subjects in the present study demonstrated good decision-making capacity regardless of consent condition so there appears no compelling need to use alternate methods of consent for healthy individuals. In contrast, participants with AD showed clearer room for improvement, and the lack of strong overall effects of the modified consent method does not diminish the urgency of fostering ethically robust means of research participation for people with AD.

It should also be noted that, depending on consent condition, approximately 30 to 45% of AD patients were deemed capable of consent. While precise rates of intact capacity have varied across studies, our findings are consistent with prior reports suggesting that a non-trivial proportion of people with AD retain capacity to consent (Karlawish et al., 2008; Kim et al., 2001; Palmer et al., 2005, 2013; Warner,

McCarney, Griffin, Hill, & Fisher, 2008). It would thus be inappropriate, and a violation of the autonomy component of the ethical principle of respect for persons, to assume that an individual with AD lacks capacity to consent based solely on diagnosis. Moreover, even among those who lack legal capacity to consent, there remains an ethical imperative to engage the individual in the decision-making process to whatever extent he or she can meaningfully engage (Black, Rabins, Sugarman, & Karlawish, 2010; Shepherd, 2016). A multi-tiered view may be more appropriate to address the issue of respecting autonomy and protection of those vulnerable to diminished capacity for autonomy in AD research. For example, a proposed multi-tiered model of consent capacity in dementia might look like this:

(1) fully capable of autonomous decision making for research;
(2) capable with support/input and advice from trusted others ("supported decision making") (Blanck & Martinis, 2015; Keeling, 2016; Peisah et al., 2013);
(3) a) incapable of consent to a particular clinical trial, even with supports, yet capable of appointing a proxy (Kim & Appelbaum, 2006; Kim et al., 2011); b) incapable of consent, but able to provide active assent/dissent; and
(4) in more severe stages of dementia, unable to engage sufficiently to provide even meaningful dissent or assent.
(Tiers 3a and 3b, as listed above, may overlap or have a reverse sequence.)

Empirical research, as well as input from key stakeholders, bioethicists, and regulatory authorities, is needed to determine how a more nuanced approach could be effectively and ethically implemented.

The overall issue of decisional incapacity has become even more salient internationally over the past decade due to the controversy around provisions in Article 12 of the U.N. Convention on the Rights of Persons with Disabilities (reviewed in Appelbaum, 2016a). Based on these provisions, some countries are discarding the notion of incapacity, i.e. all persons, regardless of disability (including those with cognitive or psychiatric disabilities), are presumed to have the right to decide for themselves about consenting to/dissenting from health and mental health care and other major life decisions. Supported decision making has been offered as a means to help those who want it to make decisions, but is not presently recognized in the current regulatory guidelines. In cogently expressing concern about completely discarding the notion of incapacity, Appelbaum (2016b) recently wrote, "We need to endorse the principles of nondiscrimination, equal access, and reasonable accommodations embodied in the document while affirming that people with severe disabilities also have rights to protection from the consequences of their condition" (unpaginated). In that vein, a more nuanced approach, incorporating multiple tiers such as those suggested above, as well as concerted efforts to optimize the consent discussions, whether through multimedia or other means, appears more respectful of the autonomy and protective components of the principle of respect for persons than is a simple binary model.

Clinical Implications

- AD is a risk factor for impaired capacity to consent to research, but it is inappropriate to assume an individual lacks such capacity based solely on their diagnosis as a sizable minority of people with mild-to-moderate AD retain decisional capacity.
- Multimedia consent does not appear to yield large improvements in comprehension of disclosed material in the context of AD (perhaps due to the rapid forgetting associated with this disorder), so the expense and burden may not be justified for studies focused on this population.
- There remains an unmet need to address *how* to meaningfully engage people with mild-to-moderate AD in the research consent or assent process. A multi-tiered model, including options such as supported decision making, and appointment of one's own proxy should be explored to further balance considerations of autonomy and protection of those with diminished capacity.

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Notes on contributors

Dr. Palmer was Principal Investigator for the primary grant that funded this project, and was the primary individual responsible for overall study design, oversight of all data collection and research staff, data analyses and interpretation, and preparation and revision of the manuscript.

Dr. Harmell was involved in data interpretation and assisted in manuscript preparation.

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