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WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological and Brain Sciences

Developmental Trajectories of Executive and Verbal Processes in Children with Phenylketonuria

by

Zoë W. Hawks

A thesis presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Master of Arts

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Washington University in St. Louis

August, 2017

ABSTRACT OF THE THESIS

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by

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Masters of Arts in Psychology

Washington University in St. Louis, 2017

Professor Desirée White, Chair

Phenylketonuria (PKU) is a recessive disorder characterized by disruption in the metabolism of the amino acid phenylalanine. Using a verbal fluency task, previous studies demonstrated that word production is reduced in individuals with PKU relative to controls. Beyond word production, verbal fluency output can be scored for clustering and switching, which enable characterization of verbal and executive processes, respectively. The present study is the first to evaluate clustering and switching in PKU within a longitudinal design, thereby elucidating the developmental time course of core cognitive processes. To this end, semantic (animals, food/drink) and phonemic (S words, F words) fluency data were obtained at three longitudinal time-points in children with early- and continuously-treated PKU ($n = 23$; 11 males, 12 females) and age-matched controls ($n = 44$; 22 males, 22 females). Age ranged from 7-19 years at the outset of the study; approximately 12-18 months elapsed between each time-point. Word production, clustering, and switching scores were analyzed using hierarchical linear modeling (HLM) to account for longitudinal dependencies and to allow evaluation of the individual contributions of age, group, and the interaction between age and group. Results indicated impairments in frontally-mediated executive processes in children with PKU relative to controls, and these impairments were exacerbated with increasing age. Additionally, children

with PKU relied more on verbal processes relative to controls, suggesting that they may use compensatory strategies to overcome executive deficits. Continued efforts to characterize cognitive development in children with PKU will inform our understanding of the disorder across the lifespan.

Introduction

Phenylketonuria (PKU) is a recessive hereditary disorder characterized by disruption in the metabolism of phenylalanine (Phe; Scriver, 2007). Unless diagnosed in infancy and thereafter managed with dietary treatment, PKU may result in severe neurologic problems and intellectual disability (Moyle, Fox, Bynevelt, Arthur, & Burnett, 2007; Paine & Hsia, 1957). Treatment notwithstanding, individuals with early- and continuously-treated PKU exhibit structural and functional brain abnormalities (Anderson & Leuzzi, 2010; Antenor-Dorsey et al., 2013; Bodner et al., 2012; Christ et al., 2016), obtain lowered scores on tests of intelligence (Ris, Williams, Hunt, Berry, & Leslie, 1994), experience psychosocial and psychiatric difficulties (Brumm, Bilder, & Waisbren, 2010; Gentile, Hoedt, & Bosch, 2010; Weglage et al., 2000), and have deficits in executive abilities (for review, see Christ, Huijbregts, de Sonnevill, & White, 2010).

The term “executive abilities” refers to a collection of higher order cognitive processes such as set shifting, working memory, strategic processing, and inhibition (Goldstein & Naglieri, 2013). Findings from typically-developing children indicate that executive abilities improve from early childhood through adolescence (Zelazo et al., 2013). In contrast, as children with PKU age, deficits in a number of executive abilities (e.g., strategic processing, working memory) become more pronounced (White, Nortz, Mandernach, Huntington, & Steiner, 2001).

The present study utilized a verbal fluency task to assess the development of executive abilities (Korkman, Kirk & Kemp, 1998) in children with PKU in comparison to typically-developing control children. During fluency tasks, participants are given one minute to generate as many words as possible belonging to a given category. Categories may be semantic (e.g., animals) or phonemic (e.g., words beginning with F). Performance is scored for number of words correct, and higher scores are thought to reflect better executive abilities.

However, “better executive abilities” is a coarse description that provides little information regarding the specific processes underlying fluency performance. To provide a more refined understanding of fluency performance, Troyer, Moscovitch, and Winocur (1997) developed a quantitative scoring system that assessed not only the number of words correct but also clustering and switching during word generation. Clusters were defined as consecutive generation of at least two words that were semantically (e.g., tiger, lion; both large felines) or phonemically (e.g., flat, flop; both beginning with fl) related. Switches were defined as transitions between semantically (e.g., lion, goldfish) or phonemically (e.g., flat, finish) unrelated words. Primary outcome measures included mean cluster size, which purportedly indexed verbal memory and word storage (i.e., verbal processes), and number of switches, which purportedly indexed strategic processes and set shifting (i.e., executive processes). Thus, the scoring procedure advanced by Troyer et al. (1997) aimed to disentangle the verbal and executive processes that contribute to fluency performance.

From a neuroanatomical perspective, research indicates that frontal brain regions largely subserve executive processes and temporal brain regions largely subserve verbal processes during verbal fluency performance. For example, in patients with frontal and temporal lobe lesions, Troyer, Moscovitch, Winocur, Alexander, and Stuss (1998a) observed an interaction between lesion location and fluency performance wherein (1) patients with frontal lobe lesions exhibited impaired switching but intact clustering relative to controls across semantic and phonemic conditions, and (2) patients with temporal lobe lesions exhibited impaired clustering and switching relative to controls in semantic conditions but intact clustering and switching in phonemic conditions. Thus, impairments in phonemic switching uniquely identified patients with frontal lobe lesions, whereas impairments in semantic clustering uniquely identified patients with

temporal lobe lesions. Converging evidence for functional specificity during clustering and switching was obtained by Hirshorn and Thompson-Schill (2006). In a study assessing semantic fluency during fMRI, they observed greater activity in the left inferior frontal gyrus during switching relative to clustering, indicating that switching is largely subserved by frontal brain regions.

More generally, evidence indicates a role for temporal brain regions in semantic processes and frontal regions in phonemic processes. For example, Grogan, Green, Ali, and Crinion (2009) observed associations between semantic fluency performance and gray matter density in the left inferior temporal cortex and associations between phonemic fluency performance and gray matter density in the pre-supplementary motor area and bilateral caudate nuclei. Regional specificity on the bases of fluency condition (i.e., semantic, phonemic) and type of cognitive processing (i.e., clustering - verbal, switching - executive) has also been observed in healthy adults (Martin, Wiggs, Lalonde, & Mack, 1994) and in patients with stroke (Baldo, Schwartz, Wilkins, & Dronkers, 2006), Parkinson disease (Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998b), Huntington disease (Ho et al., 2002), dementia of the Alzheimer type (Troyer et al., 1998b), and acquired hearing impairment (Classon, Löfkvist, Rudner, & Rönnerberg, 2014).

Of particular relevance to the present study are investigations of clustering and switching in typically-developing children and children with PKU. In typically-developing children, improvements in phonemic switching (or an experimental proxy) are consistently, positively associated with age (Kavé, Kigel, & Kochva, 2008; Koren, Kofman, & Berger, 2005; Sauzéon, Lestage, Raboutet, N'Kaoua, & Claverie, 2004). However, developmental trajectories in semantic switching and semantic and phonemic clustering are less well understood. Although

some studies reported age-related increases in semantic switching (Hurks et al., 2010; Kavé et al., 2008), others reported age-related decreases (Sauzón et al., 2004). Inconsistencies likewise pervade the developmental literature on semantic and phonemic clustering, with studies reporting age-related increases in clustering, age-related decreases in clustering, and no effect of age on clustering (Hurks et al., 2010; Kavé et al., 2008; Koren et al., 2005; Sauzón et al., 2004). These conflicting results may be attributable to variations in the definitions of clustering and switching across studies. For example, Sauzón et al. (2004) created ratios in which clustering and switching scores were scaled relative to the total number of words generated, whereas Hurks et al. (2010) used raw scores to index switching, mean cluster size, and number of clusters.

Turning to children with PKU, a number of studies have assessed word generation using verbal fluency tasks, but only one study assessed clustering and switching. Across studies of word generation, results were mixed. Whereas some studies reported impairments in phonemic (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Banerjee, Grange, Steiner, & White, 2011; Brumm et al., 2004; Channon, German, Cassina, & Lee, 2004; White, et al., 2001) and/or semantic (Banerjee et al., 2010; Brumm et al., 2004; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990) fluency, others failed to find significant effects (Anderson et al., 2007; Luciana, Hanson, & Whitley, 2004; Moyle et al., 2007; Smith, Klim, & Hanley, 2000; VanZutphen et al., 2007). In the only study to examine clustering and switching (Banerjee et al., 2010), children with PKU switched less than controls during phonemic fluency (specifically, S words and F words) and semantic fluency (specifically, Food/Drink) conditions. Additionally, there was a significant interaction between age and group for semantic fluency, indicating greater improvement in the number of switches as a function of age for controls relative to children with PKU (Banerjee et al., 2010). However, because participants were assessed only once, fine-

grained characterization of developmental changes in clustering and switching was not possible.

To overcome this limitation, we assessed clustering and switching in children with PKU and controls at three longitudinal time-points. Increased statistical power relative to prior studies of verbal fluency in PKU improved our ability to detect subtle effects. The present study is the first to investigate longitudinal change in clustering and switching in children with PKU, thereby clarifying the developmental time course of executive and verbal processes.

Quantifying verbal fluency performance

Troyer et al. (1997) stimulated researchers to consider ways in which word order might elucidate the cognitive processes underlying verbal fluency performance. However, aspects of their procedure have come under scrutiny. For example, Tröster et al. (1998) noted that switching is dependent on word generation, such that decreased word generation results in decreased opportunities to switch. To eliminate this dependency, percentage scores can be computed by dividing raw clustering and switching scores by the number of words generated (Tröster et al., 1998; Sauz on et al., 2004). In defense of raw scores, however, Troyer (2000) argued that (1) the number of switches determines the number of words generated and therefore “correcting switches for total words generated would be tantamount to correcting a cause for its effect” and (2) percentage scores fail to detect executive deficits in patient populations known to have executive deficits (Tröster et al., 1998), calling into doubt their sensitivity.

Notwithstanding, evaluating fluency performance using both raw (number of switches) and scaled (mean cluster size) measures is problematic because raw scores are highly correlated with word generation whereas scaled scores are not.

Criticism has also been levied against the characterization of raw switching as a measure of only executive abilities (Troyer et al., 1997). Abwender, Swan, Bowerman, & Connolly

(2001) suggested that increased switching reflects a failure to cluster rather than successful set shifting and therefore proposed dividing number of switches into two factorially separable subcategories: hard switching and cluster switching. Hard switching was defined as “transitions between a cluster and non-clustered words ... or between two non-clustered words” and cluster switching was defined as “transitions between adjacent ... or overlapping clusters” (Abwender et al., 2001). Mayr (2002) additionally argued that raw switching is determined by the time it takes to switch between clusters as well as the time it takes to generate words within clusters. Thus, reduced switching could reflect poorer executive abilities or, alternatively, poorer verbal memory. To quantify the relative ease of between-cluster switching compared to within-cluster word generation, Classon et al. (2014) encouraged measurement of both cluster size and number of clusters.

Traditionally, cluster size was posited to index verbal processes (Koren et al., 2005; Troyer et al., 1997), number of clusters and cluster switching were posited to index cognitive flexibility (Koren et al., 2005; Raskin & Rearick, 1996; Raskin, Sliwinski, & Borod, 1992), and hard switching was posited to index processing speed in the phonemic condition and lexical access in the semantic condition (Abwender et al., 2001). However, recent research has called into question the above interpretations of hard and cluster switching. Stemming from the observations that (1) hard switching was reduced during the second half of a verbal fluency task, suggesting an effortful, executive search process (Raboutet et al., 2010) and (2) older adults, a population with well-established executive impairments, exhibited declines in hard switching but not cluster switching relative to younger adults (Haugrud, 2012), Raboutet et al. (2010) and Haugrud (2012) proposed that hard switching reflects executive processes and cluster switching reflects verbal processes. In support of a role for frontally-mediated executive processes in hard

switching, Peter et al. (2016) observed a significant association between hard switching and gray matter volume in the left inferior frontal gyrus (IFG) during semantic fluency. Evidence is thus accruing that hard switching may index executive processes, whereas the cognitive processes underlying cluster switching remain somewhat controversial.

Experimental Approach

Synthesizing scoring methods used in the literature to date, the present study evaluated size of clusters (number of words clustered), number of clusters, and number of non-clustered words (singletons). Each cluster and singleton, excluding the word generated at the end of the list, was associated with a single switch. Therefore, number of clusters and number of singletons were characterized as switching variables (reflecting executive processes), and number of words clustered was characterized as a clustering variable (reflecting verbal processes). Together, number of words clustered, number of clusters, and number of singletons summed to equal the total number of words generated.

Our approach was largely informed by Abwender et al. (2001), with number of singletons comparable to their hard switching variable. However, inconsistent with Abwender et al. (2001), we coded a switch from a singleton to a cluster with number of clusters (cf. cluster switching) rather than number of singletons (cf. hard switching). We see two primary advantages to our approach. First, mean cluster size (as described by Troyer et al., 1997) can be derived from number of words clustered and number of clusters, facilitating comparisons between our results and previous studies of clustering and switching in child and patient populations. Second, it is unclear why the cognitive processes involved in clustering would differ following a singleton relative to a cluster. In both instances, formulating a cluster requires initiating a new semantic

network-based search process. Accordingly, our coding scheme grouped all switches to clusters together and all switches to singletons together.

In conducting our analyses, it was important to understand the effects of age and group on number of words generated before interpreting the effects of age and group on clustering and switching. As such, we first evaluated the effects of age and group on number of words correct and number of words generated. Then turning to our central focus, we decomposed number of words generated into raw clustering (number of words clustered) and raw switching (number of clusters, number of singletons) components and examined these components for associations with age and group. For the sake of thoroughness, the effects of age and group on percent clustering (percentage of words clustered) and percent switching (percentage of clusters, percentage of singletons) were also explored.

Method

Participants

Children with early- and continuously-treated PKU ($n = 23$; 11 males, 12 females) were recruited through metabolic clinics at Washington University in St. Louis and Oregon Health & Science University. All children were diagnosed in early infancy and thereafter placed on dietary treatment to limit Phe intake. No child was treated with sapropterin dihydrochloride at the time of study. Across children with PKU, mean Phe in the year preceding the study was 543.01 (SD = 274.68) $\mu\text{mol/L}$, and Phe measured closest to the start of the study was 544.06 (SD = 298.03) $\mu\text{mol/L}$.

Verbal fluency performance in children with PKU was compared to that of controls ($n = 44$; 22 males, 22 females). No child in the study had a history of major medical, psychiatric, or learning disorder unrelated to PKU. Age at the beginning of the study ranged from 7 – 18 years

($M = 12.13$, $SD = 3.31$) for children with PKU and 7 – 19 years ($M = 11.7$, $SD = 2.00$) for controls. Pertaining to race/ethnicity, < 1% of individuals with PKU and 14% of controls identified as members of a minority group. There were no significant differences between children with PKU and controls in age at baseline, gender, or race/ethnicity ($p > .05$ in all instances).

Procedure

The Verbal Fluency subtest of the NEPSY (Korkman et al., 1998) was administered at three time-points as part of a longitudinal study examining neural and cognitive outcomes in children with PKU; data related to this study have been published previously, but not in terms of longitudinal verbal fluency performance. Between visits 1 and 2, the average time elapsed was 1.09 ($SD = .29$) years for children with PKU and 1.11 ($SD = .49$) years for controls; between visits 2 and 3, the average time elapsed was 1.52 ($SD = .51$) years for children with PKU and 1.51 ($SD = .55$) years for controls.

Per NEPSY instructions, participants were given one minute to list as many words belonging to a given category as possible. There were two semantic (animal, food/drink) and two phonemic (S words, F words) categories. Each participant was assessed on all four categories, and scores were obtained as described below.

Regarding word production variables, *# words correct* was scored according to NEPSY instructions and *# words generated* was scored as the total number of word-like utterances. Regarding verbal processing variables, raw clustering was operationalized as the number of words clustered (*# words clustered*). Finally, regarding executive processing variables, raw switching was operationalized as the number of clusters (*# clusters*) and the number of singletons (*# singletons*).

As noted previously, in semantic conditions clusters were defined as groups of two or more semantically related words (e.g., shark, whale; both aquatic animals), and in phonemic conditions they were defined as groups of two or more phonemically similar words (e.g., slot, slit; which vary by a single, internal vowel sound). More detailed instructions for characterizing clusters are available in Troyer et al. (1997). Importantly, given a cluster of size N , $N - 1$ words were counted toward the score for *# words clustered*, and each cluster was counted once towards the score for *# clusters*. In the event that clusters overlapped (e.g., lion, tiger, cat, dog, goldfish; feline and pet clusters), words were not double-counted. Singletons were defined as non-clustered words; that is, words that were semantically and phonemically distinct from their neighbors. Thus, *# words clustered*, *# clusters*, and *# singletons* summed to equal *# words generated*.

Statistical approach

Analyses were conducted in R (version 0.99.893; <http://www.rstudio.com/>). The following packages were used for analyses: psych (Revelle, 2016), ggplot2 (Wickham, 2009), lme4 (Bates, Maechler, Bolker, & Walker, 2015), car (Fox & Weisberg, 2011), influence.ME (Nieuwenhuis, te Grotenhuis, & Pelzer, 2012), MuMIn (Bartoń, 2016), MASS (Venables & Ripley, 2002), and stats (R Core Team, 2016).

Given that individual fluency categories (i.e., animal, food/drink, S words, F words) are largely arbitrary and highly specific, the first step in data processing was to create semantic and phonemic composite scores. This was accomplished by summing raw scores separately within semantic (animal, food/drink) and phonemic (S words, F words) conditions for each dependent variable (*# words correct*, *# words generated*, *# words clustered*, *# clusters*, *# singletons*). Raw verbal and executive processing variables were divided by *# words generated* to derive percent

clustering (*% words clustered*) and percent switching (*% clusters, % singletons*) scores.

Descriptive statistics were calculated for all raw and percentile composites.

Next, distributions of composite scores were examined. Because all raw phonemic distributions were skewed, Box-Cox transformations were used to normalize these distributions, followed by z-score transformations ($\lambda = .26, .06, .30, .34, .14$ for *# words correct, # words generated, # words clustered, # clusters, # singletons*, respectively). Semantic and percentile distributions were normal, and therefore transformation was not necessary.

We then examined the effects of age and group on semantic and phonemic word production (*# words correct, # words generated*). Prior to analyses, outliers greater than three standard deviations from the mean of *# words correct* or *# words generated* were excluded and participant ages were grand mean centered. Given that multiple time-points were nested within individuals, hierarchical linear modeling (HLM) was used to account for longitudinal dependencies in the data. This approach has the advantage of modeling the intercept and slope (for age) separately for each individual (i.e., as random effects), which can then be examined for moderation by group. Accordingly, age was a Level 1 variable in our models and group was a Level 2 variable.

$$\text{Level 1: } Y_{ij} = \beta_{0i} + \beta_{1i} \times (\text{Age})_{ij} + e_{ij}$$

$$\text{Level 2: } \beta_{0i} = \gamma_{00} + \gamma_{01} \times (\text{Group})_i + \mu_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11} \times (\text{Group})_i + \mu_{1i}$$

The models were built in stages so that the explanatory increments of the predictors could be identified, with age entered at Step 1, group entered at Step 2, and the interaction between age and group entered at Step 3. Intercept and slope were modeled as random effects. When the

interaction between age and group was significant, a no-intercept model at Level 2 was run to determine and test the significance of simple age slopes for PKU and control groups.

As noted earlier, to evaluate verbal and executive processes, we decomposed *# words generated* into clustering (*# words clustered, % words clustered*) and switching (*# clusters, # singletons, % clusters, % singletons*) variables, respectively. For raw variables (*# words clustered, # clusters, # singletons*), we replicated the statistical modeling just described for word production variables. For percentile variables (*% words clustered, % clusters, % singletons*), we ran binomial logistic regressions using HLM; procedures were otherwise identical to those described for word production variables. Results were considered statistically significant at $p < .05$; marginal results at $p < .10$ are also reported to avoid concealment of interesting patterns of findings.

Results

To contextualize regression results and provide an overall measure of fluency performance in PKU and control groups, means and standard deviations of semantic and phonemic composite scores (collapsed across longitudinal time-point) are reported in Table 1. In addition, for the sake of clarity, results from statistical models are presented in both tabular and graphical form, the former to streamline textual descriptions and the latter to aid visualization of significant effects.

Word production

Results of HLM models are reported in Table 2. With respect to semantic fluency for *# words correct*, two results were notable. First, the effect of age was significant, indicating that *# words correct* improved as a function of increasing age. Second, although the effect of group was not significant beyond age, the interaction between age and group was significant beyond

the main effects of age and group. This indicated that *# words correct* for controls ($\gamma_{00} = 2.39$, $SE = .30$, $p < .001$) improved more as a function of age than for children with PKU ($\gamma_{01} = 1.37$, $SE = .40$, $p = .001$; Figure 1A).

With respect to semantic fluency for *# words generated*, the pattern of results was identical to that observed in semantic fluency for *# words correct*. Specifically, the effect of age was significant, the effect of group was not significant beyond age, and the interaction between age and group was significant beyond main effects of age and group. These effects were in the expected direction: *# words generated* improved as a function of increasing age, and controls ($\gamma_{00} = 3.06$, $SE = .35$, $p < .001$) improved more as a function of age than children with PKU ($\gamma_{01} = 1.42$, $SE = .47$, $p < .01$; Figure 1C).

Turning to phonemic fluency, for *# words correct*, two results were notable. First, the effect of age was significant, indicating that *# words correct* improved as a function of increasing age. Second, in contrast with results for semantic fluency, the effect of group was marginally significant beyond age, with controls generating more correct words than children with PKU (Figure 1B). The interaction between age and group was not significant beyond main effects of age and group. Taken together, these results identified age, and to a lesser extent group, as determinants of *# words correct*.

With respect to phonemic fluency for *# words generated*, the effect of age was again significant. Although the effect of group was not significant beyond age, the interaction between age and group was marginally significant beyond main effects of age and group. The effects were in the expected direction: *# words generated* improved as a function of increasing age, and controls ($\gamma_{00} = 0.20$, $SE = .03$, $p < .001$) improved more as a function of age than children with PKU ($\gamma_{01} = 0.11$, $SE = .04$, $p < .01$; Figure 1D).

Verbal processes

For *# words clustered*, the effects of age were significant across both semantic and phonemic fluency conditions, indicating that *# words clustered* increased as a function of increasing age (Table 3). Additionally, the interaction between age and group was marginally significant beyond main effects of age and group in the phonemic fluency condition, indicating that *# words clustered* increased more as a function of age for controls ($\gamma_{00} = 0.15$, $SE = .03$, $p < .001$) than children with PKU ($\gamma_{01} = 0.05$, $SE = .05$, $p = .26$; Figure 2A). Importantly, the simple slope for children with PKU did not differ significantly from zero, suggesting negligible change in *# words clustered* across the developmental period assessed. No other effects were significant for *# words clustered*.

With respect to *% words clustered* in the semantic fluency condition, the effect of age was significant, and the effect of group was marginally significant beyond the effect of age (Table 4, Figure 3A). These results indicated that *% words clustered* increased as a function of increasing age, and children with PKU produced a higher percentage of clustered words than controls. No other effects were significant for *% words clustered*.

Executive processes

For *# clusters*, the effects of age were significant across both semantic and phonemic fluency conditions, indicating that *# clusters* increased as a function of increasing age (Table 3). Additionally, the interaction between age and group was significant beyond main effects of age and group in the phonemic fluency condition, indicating that *# clusters* increased more as a function of age for controls ($\gamma_{00} = 0.16$, $SE = .03$, $p < .001$) than children with PKU ($\gamma_{01} = 0.04$, $SE = 0.05$, $p = .39$; Figure 2B). The simple slope for children with PKU did not differ

significantly from zero, suggesting no change in *# clusters* across the developmental period. No other effects were significant for *# clusters*.

With respect to *# singletons*, in the semantic fluency condition the effect of age was significant, the effect of group was significant beyond the effect of age, and the interaction between age and group was marginally significant beyond main effects of age and group (Table 3). These results indicated that *# singletons* increased as a function of increasing age, controls produced more singletons than children with PKU, and production of singletons by controls ($\gamma_{00} = 0.53, SE = .17, p < .01$) increased more as a function of age than for children with PKU ($\gamma_{01} = -0.02, SE = .22, p = .92$; Figures 2C and 2D). Consistent with patterns observed for *# words clustered* and *# clusters*, the simple slope for PKU participants did not differ significantly from zero, suggesting negligible change in *# singletons* across the developmental period.

In the phonemic fluency condition, the effect of age on *# singletons* was significant, and the effect of group was marginally significant beyond the effect of age. As in the semantic fluency condition, these results indicated that *# singletons* increased as a function of increasing age, and controls produced more singletons than children with PKU. No other effects were significant for *# singletons*.

With respect to *% singletons*, in the semantic fluency condition the effect of group was significant beyond the effect of age, indicating that controls produced a higher percentage of singletons than children with PKU (Table 4, Figure 3B). No other effects of percentile switching variables (*% singletons*, *% clusters*) were significant.

Discussion

The present study focused on developmental trajectories of verbal and executive processes in children with PKU by examining word production, clustering, and switching during

semantic and phonemic conditions of a verbal fluency task. Clustering and switching were evaluated both as raw and percentile scores. Data were analyzed using hierarchical linear modeling (HLM) to account for longitudinal dependencies and to allow evaluation of the individual contributions of age, group, and the interaction between age and group.

Although the main effect of group and the interaction between age and group are most interesting when comparing verbal fluency performance in children with PKU to that of controls, we first address the main effect of age. Age emerged as an important determinant of raw scores (i.e., word production, executive processes, verbal processes) irrespective of fluency condition (i.e., semantic, phonemic), indicating that raw performance improved as a function of increasing age. Regarding percentile variables, it is important to keep in mind that these variables are interdependent. That is, if executive processes are utilized to a relatively greater degree, then verbal processes will be utilized to a relatively lesser degree (and vice versa). With a single exception (semantic clustering), age did not explain significant variance in percentile scores, indicating that the relative contributions of executive and verbal processes to fluency performance remained stable across development.

With respect to group, this variable emerged as a significant predictor of word production in the phonemic condition, with controls producing more correct words than children with PKU. This difference in overall performance appears to be at least partially attributable to group differences in executive processes, as controls generated more singletons than children with PKU. Singleton production also distinguished controls from children with PKU in percentile data. Specifically, in the semantic condition, controls produced a higher percentage of singletons than children with PKU, whereas children with PKU produced a higher percentage of clustered words. This trade-off suggests that children with PKU relied more on verbal processes during

semantic fluency (Koren et al., 2005; Troyer et al., 1997), whereas controls relied more on frontally-mediated executive processes (Raboutet et al., 2010; Haugrud, 2012; Peter et al., 2016). Given group differences in raw singleton scores, indicative of executive impairment in children with PKU, overreliance on verbal processes by children with PKU might be interpreted as a compensatory strategy. However, further research is needed to rigorously test this hypothesis. Likewise, it remains unclear why group effects in percentile data emerged for semantic but not phonemic fluency. Due to greater frontal-executive burden associated with phonemic fluency relative to semantic fluency (Grogan et al., 2009; Martin et al., 1994; Baldo et al., 2006), we suggest that compensatory verbal processes may be more difficult to implement during phonemic fluency tasks, but additional research is needed to evaluate this conjecture fully.

Having characterized age and group effects, we turned our attention to the interaction between age and group. This interaction was of particular interest due to its bearing on executive and verbal developmental trajectories. With respect to word production, the interaction between age and group emerged as an important predictor of performance across both semantic and phonemic conditions, indicating that controls improved more as a function of age than children with PKU. Additionally, with respect to executive and verbal processes, the interaction between age and group emerged as an important predictor of clustering and switching. This effect was most commonly observed in the phonemic fluency condition and suggests more rapid development of both executive and verbal processes in controls relative to children with PKU, thereby exacerbating preexisting group differences. Recalling the role of the prefrontal cortex in subserving phonemic fluency (Grogan et al., 2009; Martin et al., 1994; Baldo et al., 2006), these results are consistent with a frontally-mediated executive deficit in children with PKU.

Critically, post-hoc analyses of simple age slopes for children with PKU indicated negligible improvement in both executive and verbal processes. Specifically, simple age slopes for children with PKU were statistically equivalent to zero for phonemic clustering, phonemic switching, and semantic switching. In contrast, controls exhibited significant increases in these variables with age. As such, developmental trajectories in frontally-mediated switching (Raboutet et al., 2010; Haugrud, 2012; Peter et al., 2016) and phonemic (Grogan et al., 2009; Martin et al., 1994; Baldo et al., 2006) processes were stagnant for children with PKU but continued to improve for controls during childhood, resulting in an ever-widening performance gap.

In terms of limitations, the present study employed a relatively coarse timing method, in which participants were provided one minute to generate as many words as possible. It has been suggested that decreased switching during the latter portion of verbal fluency tasks reflects executive processes (Crowe, 1998; Hurks et al., 2010). Thus, it would be informative to evaluate trajectories in clustering and switching during verbal fluency as a function of elapsed time, age, and group. However, doing so would require a time stamp for each word generated, which we did not collect. The present study was also limited by inconsistencies in extant literature regarding (1) the measurement of and (2) the cognitive processes underlying clustering and switching. Although consensus is accruing that clustering indexes verbal processes (Koren et al., 2005; Raskin & Rearick, 1996; Raskin et al., 1992) and switching indexes executive processes (Raboutet et al., 2010; Haugrud, 2012; Peter et al., 2016), converging evidence from multiple tasks would make a stronger argument for the impaired development of executive abilities in children with PKU.

Conclusion

Our results indicate that children with early and continuously-treated PKU exhibit impairments in frontally-mediated executive processes relative to typically-developing control children. Moreover, interactions between age and group indicate that these executive impairments become more pronounced as children with PKU grow older, engendering an ever-widening difference between the performance of children with PKU and controls. Finally, individuals with PKU relied more heavily on verbal processes relative to controls, suggesting that they may use verbal strategies to compensate for executive deficits.

These results have practical implications in terms of cognitive interventions for children with PKU. First, they underscore the need to monitor cognition in children with PKU beyond early childhood, as executive impairments became more pronounced during adolescence. Second, they designate verbal processes as relatively intact, suggesting that adaptive functioning may be improved by interventions that play to this strength. Continued efforts to characterize cognitive development in not only children but also adults with PKU will inform our understanding of the disorder across the lifespan.

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Tables and Figures

Table 1. Mean (standard deviation) of semantic and phonemic composite scores, collapsed across longitudinal time-point.

	Semantic		Phonemic	
	PKU	Control	PKU	Control
# Words Correct	38.04 (9.8)	38.95 (10.3)	19.13 (6.3)	23.09 (9.5)
# Words Generated	44.25 (10.4)	44.98 (11.5)	25.52 (7.3)	28.97 (10.0)
# Words Clustered	23.15 (9.3)	21.98 (8.1)	7.43 (4.8)	8.42 (5.0)
# Clusters	11.29 (3.3)	10.85 (3.0)	4.92 (2.6)	5.62 (3.0)
# Singletons	9.56 (4.3)	12.09 (5.8)	13.15 (4.0)	14.92 (6.2)
% Words Clustered	0.51 (.11)	0.48 (.11)	0.27 (.11)	0.28 (.12)
% Clusters	0.26 (.06)	0.24 (.04)	0.19 (.07)	0.19 (.06)
% Singletons	0.23 (.11)	0.27 (.12)	0.54 (.17)	0.53 (.17)

Table 2. HLM models for raw word production variables.

	# Words Correct						# Words Generated					
	Semantic			Phonemic			Semantic			Phonemic		
	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
Intercept	38.83*** (0.86)	39.29*** (1.04)	39.62*** (1.06)	0.03 (0.10)	0.14 (0.11)	0.18 (0.11)	45.33*** (1.01)	45.46*** (1.22)	46.27*** (1.28)	0.02 (0.10)	0.11 (0.12)	0.15 (0.12)
Age	2.03*** (0.24)	2.03*** (0.24)	2.39*** (0.30)	0.19*** (0.03)	0.18*** (0.02)	0.21*** (0.03)	2.45*** (0.28)	2.45*** (0.28)	3.06*** (0.35)	0.18*** (0.03)	0.17*** (0.02)	0.20*** (0.03)
Group		-1.43 (1.75)	-2.23 (1.81)		-0.35 [†] (0.18)	-0.46** (0.19)		-0.41 (1.95)	-2.63 (2.17)		-0.26 (0.19)	-0.38 [†] (0.20)
Age x Group			-1.02** (0.50)			-0.08 (0.05)			-1.64*** (0.59)			-0.10 [†] (0.05)
Observations	199	199	199	200	200	200	199	199	199	200	200	200
Outliers (obs.)	2	2	2	1	1	1	2	2	2	1	1	1
Akaike Inf. Crit.	1,385.44	1,383.84	1,381.41	467.63	467.71	471.52	1,423.73	1,422.52	1,416.53	467.88	469.72	472.45
Bayesian Inf. Crit.	1,405.20	1,406.90	1,407.76	487.41	490.79	497.9	1,443.49	1,445.57	1,442.88	487.67	492.81	498.84
Likelihood ratio test (χ^2)		0.67	3.96*		3.57 [†]	2.39		0.05	7.11**		1.65	3.50 [†]

Notes: [†]p<0.1; *p<0.05; **p<0.01; ***p<0.001; preferred models, identified using likelihood ratio test, are outlined in black

Table 3. HLM models for raw executive and verbal processing variables.

	# Words Clustered						# Clusters						# Singletons					
	Semantic			Phonemic			Semantic			Phonemic			Semantic			Phonemic		
	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
Intercept	22.35*** (0.70)	22.19*** (0.86)	22.42*** (0.88)	0.04 (0.10)	0.08 (0.12)	0.11 (0.12)	11.04*** (0.25)	10.96*** (0.31)	10.98*** (0.32)	0.04 (0.09)	0.09 (0.11)	0.13 (0.11)	11.17*** (0.46)	11.93*** (0.55)	11.99*** (0.55)	0.02 (0.08)	0.13 (0.10)	0.14 (0.10)
Age	1.28*** (0.21)	1.28*** (0.21)	1.50*** (0.26)	0.12*** (0.03)	0.12*** (0.03)	0.15*** (0.03)	0.47*** (0.08)	0.47*** (0.08)	0.49*** (0.10)	0.12*** (0.03)	0.12*** (0.03)	0.16*** (0.03)	0.33** (0.14)	0.32** (0.14)	0.53*** (0.17)	0.11*** (0.02)	0.12*** (0.02)	0.13*** (0.03)
Group		0.50 (1.44)	-0.04 (1.50)		-0.13 (0.20)	-0.23 (0.20)		0.24 (0.53)	0.20 (0.54)		-0.15 (0.18)	-0.28 (0.19)		-2.35** (0.94)	-2.35** (0.94)		-0.31* (0.17)	-0.32* (0.17)
Age x Group			-0.69 (0.45)			-0.10* (0.06)			-0.07 (0.16)			-0.12** (0.06)			-0.55** (0.28)			-0.04 (0.05)
Observations	195	195	195	197	197	197	196	196	196	197	197	197	194	194	194	195	195	195
Outliers (obs.)	6	6	6	4	4	4	5	5	5	4	4	4	7	7	7	6	6	6
Akaike Inf. Crit.	1,315.12	1,314.45	1,313.96	524.08	527.12	530.19	956.51	957.75	961.37	537.03	540.01	541.94	1,182.69	1,177.64	1,176.61	513.69	514.24	519.64
Bayesian Inf. Crit.	1,334.76	1,337.36	1,340.15	543.78	550.1	556.45	976.18	980.7	987.59	556.73	563	568.2	1,202.30	1,200.52	1,202.76	533.33	537.15	545.82
Likelihood ratio test (χ^2)		0.12	2.21		0.40	2.98 ^f		0.22	0.16		0.62	4.17*		5.50*	3.84 ^d		3.23 ^e	0.79

Notes: ¹p²p³p⁴p⁵p⁶p⁷p⁸p⁹p¹⁰p¹¹p¹²p¹³p¹⁴p¹⁵p¹⁶p¹⁷p¹⁸p¹⁹p²⁰p²¹p²²p²³p²⁴p²⁵p²⁶p²⁷p²⁸p²⁹p³⁰p³¹p³²p³³p³⁴p³⁵p³⁶p³⁷p³⁸p³⁹p⁴⁰p⁴¹p⁴²p⁴³p⁴⁴p⁴⁵p⁴⁶p⁴⁷p⁴⁸p⁴⁹p⁵⁰p⁵¹p⁵²p⁵³p⁵⁴p⁵⁵p⁵⁶p⁵⁷p⁵⁸p⁵⁹p⁶⁰p⁶¹p⁶²p⁶³p⁶⁴p⁶⁵p⁶⁶p⁶⁷p⁶⁸p⁶⁹p⁷⁰p⁷¹p⁷²p⁷³p⁷⁴p⁷⁵p⁷⁶p⁷⁷p⁷⁸p⁷⁹p⁸⁰p⁸¹p⁸²p⁸³p⁸⁴p⁸⁵p⁸⁶p⁸⁷p⁸⁸p⁸⁹p⁹⁰p⁹¹p⁹²p⁹³p⁹⁴p⁹⁵p⁹⁶p⁹⁷p⁹⁸p⁹⁹p¹⁰⁰p¹⁰¹p¹⁰²p¹⁰³p¹⁰⁴p¹⁰⁵p¹⁰⁶p¹⁰⁷p¹⁰⁸p¹⁰⁹p¹¹⁰p¹¹¹p¹¹²p¹¹³p¹¹⁴p¹¹⁵p¹¹⁶p¹¹⁷p¹¹⁸p¹¹⁹p¹²⁰p¹²¹p¹²²p¹²³p¹²⁴p¹²⁵p¹²⁶p¹²⁷p¹²⁸p¹²⁹p¹³⁰p¹³¹p¹³²p¹³³p¹³⁴p¹³⁵p¹³⁶p¹³⁷p¹³⁸p¹³⁹p¹⁴⁰p¹⁴¹p¹⁴²p¹⁴³p¹⁴⁴p¹⁴⁵p¹⁴⁶p¹⁴⁷p¹⁴⁸p¹⁴⁹p¹⁵⁰p¹⁵¹p¹⁵²p¹⁵³p¹⁵⁴p¹⁵⁵p¹⁵⁶p¹⁵⁷p¹⁵⁸p¹⁵⁹p¹⁶⁰p¹⁶¹p¹⁶²p¹⁶³p¹⁶⁴p¹⁶⁵p¹⁶⁶p¹⁶⁷p¹⁶⁸p¹⁶⁹p¹⁷⁰p¹⁷¹p¹⁷²p¹⁷³p¹⁷⁴p¹⁷⁵p¹⁷⁶p¹⁷⁷p¹⁷⁸p¹⁷⁹p¹⁸⁰p¹⁸¹p¹⁸²p¹⁸³p¹⁸⁴p¹⁸⁵p¹⁸⁶p¹⁸⁷p¹⁸⁸p¹⁸⁹p¹⁹⁰p¹⁹¹p¹⁹²p¹⁹³p¹⁹⁴p¹⁹⁵p¹⁹⁶p¹⁹⁷p¹⁹⁸p¹⁹⁹p²⁰⁰p²⁰¹p²⁰²p²⁰³p²⁰⁴p²⁰⁵p²⁰⁶p²⁰⁷p²⁰⁸p²⁰⁹p²¹⁰p²¹¹p²¹²p²¹³p²¹⁴p²¹⁵p²¹⁶p²¹⁷p²¹⁸p²¹⁹p²²⁰p²²¹p²²²p²²³p²²⁴p²²⁵p²²⁶p²²⁷p²²⁸p²²⁹p²³⁰p²³¹p²³²p²³³p²³⁴p²³⁵p²³⁶p²³⁷p²³⁸p²³⁹p²⁴⁰p²⁴¹p²⁴²p²⁴³p²⁴⁴p²⁴⁵p²⁴⁶p²⁴⁷p²⁴⁸p²⁴⁹p²⁵⁰p²⁵¹p²⁵²p²⁵³p²⁵⁴p²⁵⁵p²⁵⁶p²⁵⁷p²⁵⁸p²⁵⁹p²⁶⁰p²⁶¹p²⁶²p²⁶³p²⁶⁴p²⁶⁵p²⁶⁶p²⁶⁷p²⁶⁸p²⁶⁹p²⁷⁰p²⁷¹p²⁷²p²⁷³p²⁷⁴p²⁷⁵p²⁷⁶p²⁷⁷p²⁷⁸p²⁷⁹p²⁸⁰p²⁸¹p²⁸²p²⁸³p²⁸⁴p²⁸⁵p²⁸⁶p²⁸⁷p²⁸⁸p²⁸⁹p²⁹⁰p²⁹¹p²⁹²p²⁹³p²⁹⁴p²⁹⁵p²⁹⁶p²⁹⁷p²⁹⁸p²⁹⁹p³⁰⁰p³⁰¹p³⁰²p³⁰³p³⁰⁴p³⁰⁵p³⁰⁶p³⁰⁷p³⁰⁸p³⁰⁹p³¹⁰p³¹¹p³¹²p³¹³p³¹⁴p³¹⁵p³¹⁶p³¹⁷p³¹⁸p³¹⁹p³²⁰p³²¹p³²²p³²³p³²⁴p³²⁵p³²⁶p³²⁷p³²⁸p³²⁹p³³⁰p³³¹p³³²p³³³p³³⁴p³³⁵p³³⁶p³³⁷p³³⁸p³³⁹p³⁴⁰p³⁴¹p³⁴²p³⁴³p³⁴⁴p³⁴⁵p³⁴⁶p³⁴⁷p³⁴⁸p³⁴⁹p³⁵⁰p³⁵¹p³⁵²p³⁵³p³⁵⁴p³⁵⁵p³⁵⁶p³⁵⁷p³⁵⁸p³⁵⁹p³⁶⁰p³⁶¹p³⁶²p³⁶³p³⁶⁴p³⁶⁵p³⁶⁶p³⁶⁷p³⁶⁸p³⁶⁹p³⁷⁰p³⁷¹p³⁷²p³⁷³p³⁷⁴p³⁷⁵p³⁷⁶p³⁷⁷p³⁷⁸p³⁷⁹p³⁸⁰p³⁸¹p³⁸²p³⁸³p³⁸⁴p³⁸⁵p³⁸⁶p³⁸⁷p³⁸⁸p³⁸⁹p³⁹⁰p³⁹¹p³⁹²p³⁹³p³⁹⁴p³⁹⁵p³⁹⁶p³⁹⁷p³⁹⁸p³⁹⁹p⁴⁰⁰p⁴⁰¹p⁴⁰²p⁴⁰³p⁴⁰⁴p⁴⁰⁵p⁴⁰⁶p⁴⁰⁷p⁴⁰⁸p⁴⁰⁹p⁴¹⁰p⁴¹¹p⁴¹²p⁴¹³p⁴¹⁴p⁴¹⁵p⁴¹⁶p⁴¹⁷p⁴¹⁸p⁴¹⁹p⁴²⁰p⁴²¹p⁴²²p⁴²³p⁴²⁴p⁴²⁵p⁴²⁶p⁴²⁷p⁴²⁸p⁴²⁹p⁴³⁰p⁴³¹p⁴³²p⁴³³p⁴³⁴p⁴³⁵p⁴³⁶p⁴³⁷p⁴³⁸p⁴³⁹p⁴⁴⁰p⁴⁴¹p⁴⁴²p⁴⁴³p⁴⁴⁴p⁴⁴⁵p⁴⁴⁶p⁴⁴⁷p⁴⁴⁸p⁴⁴⁹p⁴⁵⁰p⁴⁵¹p⁴⁵²p⁴⁵³p⁴⁵⁴p⁴⁵⁵p⁴⁵⁶p⁴⁵⁷p⁴⁵⁸p⁴⁵⁹p⁴⁶⁰p⁴⁶¹p⁴⁶²p⁴⁶³p⁴⁶⁴p⁴⁶⁵p⁴⁶⁶p⁴⁶⁷p⁴⁶⁸p⁴⁶⁹p⁴⁷⁰p⁴⁷¹p⁴⁷²p⁴⁷³p⁴⁷⁴p⁴⁷⁵p⁴⁷⁶p⁴⁷⁷p⁴⁷⁸p⁴⁷⁹p⁴⁸⁰p⁴⁸¹p⁴⁸²p⁴⁸³p⁴⁸⁴p⁴⁸⁵p⁴⁸⁶p⁴⁸⁷p⁴⁸⁸p⁴⁸⁹p⁴⁹⁰p⁴⁹¹p⁴⁹²p⁴⁹³p⁴⁹⁴p⁴⁹⁵p⁴⁹⁶p⁴⁹⁷p⁴⁹⁸p⁴⁹⁹p⁵⁰⁰p⁵⁰¹p⁵⁰²p⁵⁰³p⁵⁰⁴p⁵⁰⁵p⁵⁰⁶p⁵⁰⁷p⁵⁰⁸p⁵⁰⁹p⁵¹⁰p⁵¹¹p⁵¹²p⁵¹³p⁵¹⁴p⁵¹⁵p⁵¹⁶p⁵¹⁷p⁵¹⁸p⁵¹⁹p⁵²⁰p⁵²¹p⁵²²p⁵²³p⁵²⁴p⁵²⁵p⁵²⁶p⁵²⁷p⁵²⁸p⁵²⁹p⁵³⁰p⁵³¹p⁵³²p⁵³³p⁵³⁴p⁵³⁵p⁵³⁶p⁵³⁷p⁵³⁸p⁵³⁹p⁵⁴⁰p⁵⁴¹p⁵⁴²p⁵⁴³p⁵⁴⁴p⁵⁴⁵p⁵⁴⁶p⁵⁴⁷p⁵⁴⁸p⁵⁴⁹p⁵⁵⁰p⁵⁵¹p⁵⁵²p⁵⁵³p⁵⁵⁴p⁵⁵⁵p⁵⁵⁶p⁵⁵⁷p⁵⁵⁸p⁵⁵⁹p⁵⁶⁰p⁵⁶¹p⁵⁶²p⁵⁶³p⁵⁶⁴p⁵⁶⁵p⁵⁶⁶p⁵⁶⁷p⁵⁶⁸p⁵⁶⁹p⁵⁷⁰p⁵⁷¹p⁵⁷²p⁵⁷³p⁵⁷⁴p⁵⁷⁵p⁵⁷⁶p⁵⁷⁷p⁵⁷⁸p⁵⁷⁹p⁵⁸⁰p⁵⁸¹p⁵⁸²p⁵⁸³p⁵⁸⁴p⁵⁸⁵p⁵⁸⁶p⁵⁸⁷p⁵⁸⁸p⁵⁸⁹p⁵⁹⁰p⁵⁹¹p⁵⁹²p⁵⁹³p⁵⁹⁴p⁵⁹⁵p⁵⁹⁶p⁵⁹⁷p⁵⁹⁸p⁵⁹⁹p⁶⁰⁰p⁶⁰¹p⁶⁰²p⁶⁰³p⁶⁰⁴p⁶⁰⁵p⁶⁰⁶p⁶⁰⁷p⁶⁰⁸p⁶⁰⁹p⁶¹⁰p⁶¹¹p⁶¹²p⁶¹³p⁶¹⁴p⁶¹⁵p⁶¹⁶p⁶¹⁷p⁶¹⁸p⁶¹⁹p⁶²⁰p⁶²¹p⁶²²p⁶²³p⁶²⁴p⁶²⁵p⁶²⁶p⁶²⁷p⁶²⁸p⁶²⁹p⁶³⁰p⁶³¹p⁶³²p⁶³³p⁶³⁴p⁶³⁵p⁶³⁶p⁶³⁷p⁶³⁸p⁶³⁹p⁶⁴⁰p⁶⁴¹p⁶⁴²p⁶⁴³p⁶⁴⁴p⁶⁴⁵p⁶⁴⁶p⁶⁴⁷p⁶⁴⁸p⁶⁴⁹p⁶⁵⁰p⁶⁵¹p⁶⁵²p⁶⁵³p⁶⁵⁴p⁶⁵⁵p⁶⁵⁶p⁶⁵⁷p⁶⁵⁸p⁶⁵⁹p⁶⁶⁰p⁶⁶¹p⁶⁶²p⁶⁶³p⁶⁶⁴p⁶⁶⁵p⁶⁶⁶p⁶⁶⁷p⁶⁶⁸p⁶⁶⁹p⁶⁷⁰p⁶⁷¹p⁶⁷²p⁶⁷³p⁶⁷⁴p⁶⁷⁵p⁶⁷⁶p⁶⁷⁷p⁶⁷⁸p⁶⁷⁹p⁶⁸⁰p⁶⁸¹p⁶⁸²p⁶⁸³p⁶⁸⁴p⁶⁸⁵p⁶⁸⁶p⁶⁸⁷p⁶⁸⁸p⁶⁸⁹p⁶⁹⁰p⁶⁹¹p⁶⁹²p⁶⁹³p⁶⁹⁴p⁶⁹⁵p⁶⁹⁶p⁶⁹⁷p⁶⁹⁸p⁶⁹⁹p⁷⁰⁰p⁷⁰¹p⁷⁰²p⁷⁰³p⁷⁰⁴p⁷⁰⁵p⁷⁰⁶p⁷⁰⁷p⁷⁰⁸p⁷⁰⁹p⁷¹⁰p⁷¹¹p⁷¹²p⁷¹³p⁷¹⁴p⁷¹⁵p⁷¹⁶p⁷¹⁷p⁷¹⁸p⁷¹⁹p⁷²⁰p⁷²¹p⁷²²p⁷²³p⁷²⁴p⁷²⁵p⁷²⁶p⁷²⁷p⁷²⁸p⁷²⁹p⁷³⁰p⁷³¹p⁷³²p⁷³³p⁷³⁴p⁷³⁵p⁷³⁶p⁷³⁷p⁷³⁸p⁷³⁹p⁷⁴⁰p⁷⁴¹p⁷⁴²p⁷⁴³p⁷⁴⁴p⁷⁴⁵p⁷⁴⁶p⁷⁴⁷p⁷⁴⁸p⁷⁴⁹p⁷⁵⁰p⁷⁵¹p⁷⁵²p⁷⁵³p⁷⁵⁴p⁷⁵⁵p⁷⁵⁶p⁷⁵⁷p⁷⁵⁸p⁷⁵⁹p⁷⁶⁰p⁷⁶¹p⁷⁶²p⁷⁶³p⁷⁶⁴p⁷⁶⁵p⁷⁶⁶p⁷⁶⁷p⁷⁶⁸p⁷⁶⁹p⁷⁷⁰p⁷⁷¹p⁷⁷²p⁷⁷³p⁷⁷⁴p⁷⁷⁵p⁷⁷⁶p⁷⁷⁷p⁷⁷⁸p⁷⁷⁹p⁷⁸⁰p⁷⁸¹p⁷⁸²p⁷⁸³p⁷⁸⁴p⁷⁸⁵p⁷⁸⁶p⁷⁸⁷p⁷⁸⁸p⁷⁸⁹p⁷⁹⁰p⁷⁹¹p⁷⁹²p⁷⁹³p⁷⁹⁴p⁷⁹⁵p⁷⁹⁶p⁷⁹⁷p⁷⁹⁸p⁷⁹⁹p⁸⁰⁰p⁸⁰¹p⁸⁰²p⁸⁰³p⁸⁰⁴p⁸⁰⁵p⁸⁰⁶p⁸⁰⁷p⁸⁰⁸p⁸⁰⁹p⁸¹⁰p⁸¹¹p⁸¹²p⁸¹³p⁸¹⁴p⁸¹⁵p⁸¹⁶p⁸¹⁷p⁸¹⁸p⁸¹⁹p⁸²⁰p⁸²¹p⁸²²p⁸²³p⁸²⁴p⁸²⁵p⁸²⁶p⁸²⁷p⁸²⁸p⁸²⁹p⁸³⁰p⁸³¹p⁸³²p⁸³³p⁸³⁴p⁸³⁵p⁸³⁶p⁸³⁷p⁸³⁸p⁸³⁹p⁸⁴⁰p⁸⁴¹p⁸⁴²p⁸⁴³p⁸⁴⁴p⁸⁴⁵p⁸⁴⁶p⁸⁴⁷p⁸⁴⁸p⁸⁴⁹p⁸⁵⁰p⁸⁵¹p⁸⁵²p⁸⁵³p⁸⁵⁴p⁸⁵⁵p⁸⁵⁶p⁸⁵⁷p⁸⁵⁸p⁸⁵⁹p⁸⁶⁰p⁸⁶¹p⁸⁶²p⁸⁶³p⁸⁶⁴p⁸⁶⁵p⁸⁶⁶p⁸⁶⁷p⁸⁶⁸p⁸⁶⁹p⁸⁷⁰p⁸⁷¹p⁸⁷²p⁸⁷³p⁸⁷⁴p⁸⁷⁵p⁸⁷⁶p⁸⁷⁷p⁸⁷⁸p⁸⁷⁹p⁸⁸⁰p⁸⁸¹p⁸⁸²p⁸⁸³p⁸⁸⁴p⁸⁸⁵p⁸⁸⁶p⁸⁸⁷p⁸⁸⁸p⁸⁸⁹p⁸⁹⁰p⁸⁹¹p⁸⁹²p⁸⁹³p⁸⁹⁴p⁸⁹⁵p⁸⁹⁶p⁸⁹⁷p⁸⁹⁸p⁸⁹⁹p⁹⁰⁰p⁹⁰¹p⁹⁰²p⁹⁰³p⁹⁰⁴p⁹⁰⁵p⁹⁰⁶p⁹⁰⁷p⁹⁰⁸p⁹⁰⁹p⁹¹⁰p⁹¹¹p⁹¹²p⁹¹³p⁹¹⁴p⁹¹⁵p⁹¹⁶p⁹¹⁷p⁹¹⁸p⁹¹⁹p⁹²⁰p⁹²¹p⁹²²p⁹²³p⁹²⁴p⁹²⁵p⁹²⁶p⁹²⁷p⁹²⁸p⁹²⁹p⁹³⁰p⁹³¹p⁹³²p⁹³³p⁹³⁴p⁹³⁵p⁹³⁶p⁹³⁷p⁹³⁸p⁹³⁹p⁹⁴⁰p⁹⁴¹p⁹⁴²p⁹⁴³p⁹⁴⁴p⁹⁴⁵p⁹⁴⁶p⁹⁴⁷p⁹⁴⁸p⁹⁴⁹p⁹⁵⁰p⁹⁵¹p⁹⁵²p⁹⁵³p⁹⁵⁴p⁹⁵⁵p⁹⁵⁶p⁹⁵⁷p⁹⁵⁸p⁹⁵⁹p⁹⁶⁰p⁹⁶¹p⁹⁶²p⁹⁶³p⁹⁶⁴p⁹⁶⁵p⁹⁶⁶p⁹⁶⁷p⁹⁶⁸p⁹⁶⁹p⁹⁷⁰p⁹⁷¹p⁹⁷²p⁹⁷³p⁹⁷⁴p⁹⁷⁵p⁹⁷⁶p⁹⁷⁷p⁹⁷⁸p⁹⁷⁹p⁹⁸⁰p⁹⁸¹p⁹⁸²p⁹⁸³p⁹⁸⁴p⁹⁸⁵p⁹⁸⁶p⁹⁸⁷p⁹⁸⁸p⁹⁸⁹p⁹⁹⁰p⁹⁹¹p⁹⁹²p⁹⁹³p⁹⁹⁴p⁹⁹⁵p⁹⁹⁶p⁹⁹⁷p⁹⁹⁸p⁹⁹⁹p¹⁰⁰⁰

Table 4. HLM models for percentage executive and verbal processing variables.

	% Words Clustered						% Clusters						% Singletons					
	Semantic			Phonemic			Semantic			Phonemic			Semantic			Phonemic		
	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
Intercept	-0.01 (0.04)	-0.05 (0.04)	-0.05 (0.04)	-0.95*** (0.05)	-0.94*** (0.06)	-0.93*** (0.06)	-1.12*** (0.03)	-1.14*** (0.03)	-1.14*** (0.03)	-1.42*** (0.04)	-1.42*** (0.04)	-1.42*** (0.04)	-1.11*** (0.06)	-1.02*** (0.07)	-1.03*** (0.07)	0.05 (0.06)	0.03 (0.08)	0.02 (0.08)
Age	0.02* (0.01)	0.02* (0.01)	0.02 (0.02)	0.01 (0.02)	0.01 (0.02)	0.02 (0.02)	-0.003 (0.01)	-0.003 (0.01)	-0.01 (0.01)	-0.003 (0.01)	-0.003 (0.01)	0.01 (0.02)	-0.01 (0.02)	-0.01 (0.02)	-0.001 (0.02)	-0.02 (0.02)	-0.02 (0.02)	-0.03 (0.03)
Group		0.13* (0.07)	0.13* (0.08)		-0.02 (0.11)	-0.03 (0.11)		0.06 (0.05)	0.06 (0.05)		-0.001 (0.08)	-0.001 (0.08)		-0.29** (0.12)	-0.27** (0.12)		0.06 (0.13)	0.08 (0.13)
Age x Group			0.001 (0.03)			-0.03 (0.03)			0.01 (0.02)						-0.03 (0.04)			0.03 (0.04)
Observations	197	197	197	196	196	196	195	195	195	197	197	197	194	194	194	196	196	196
Outliers (obs.)	4	4	4	5	5	5	6	6	6	4	4	4	7	7	7	5	5	5
Akaike Inf. Crit.	1,151.06	1,149.94	1,151.94	981.41	983.39	984.37	858.25	858.95	860.53	783.54	785.54	786.76	1,206.19	1,202.63	1,204.09	1,183.79	1,185.57	1,187.11
Bayesian Inf. Crit.	1,167.47	1,169.64	1,174.92	997.8	1,003.06	1,007.32	874.62	878.59	883.44	799.96	805.24	809.74	1,222.52	1,222.23	1,226.97	1,200.18	1,205.24	1,210.06
Likelihood ratio test (χ^2)		3.12 [†]	0.00		0.02	1.02		1.30	0.42		0.00	0.78		5.56*	0.47		0.64	0.50

Notes: [†]p*[†]p**p***p<0.01; preferred models, identified using likelihood ratio test, are outlined in black

Figure 1. Significant ($p < .05$) and marginally significant ($p < .10$) effects of group and age x group on word production data. Graphs plot data prior to normalization, standardization, and centering.

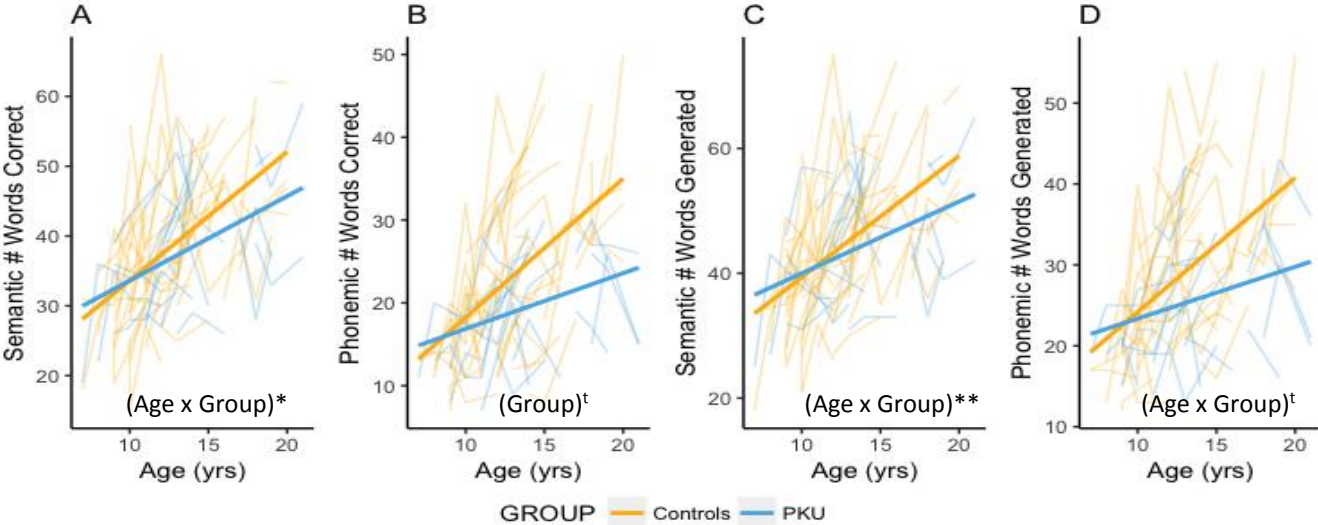


Figure 2. Significant ($p < .05$) and marginally significant ($p < .10$) effects of group and age x group on raw clustering and switching data. Graphs plot data prior to normalization, standardization, and centering.

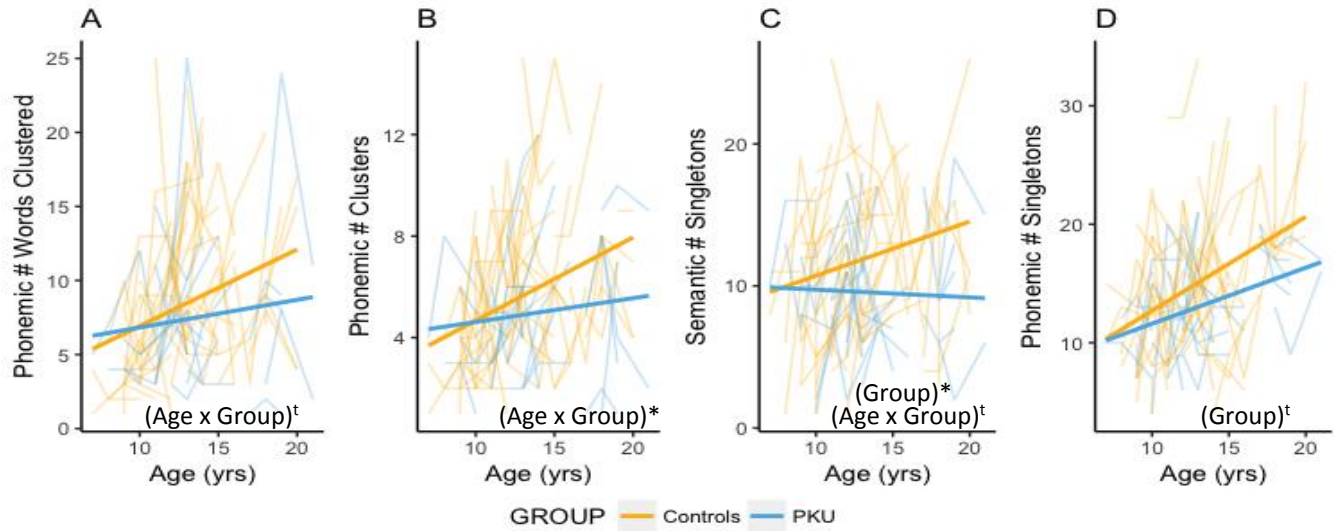


Figure 3. Significant ($p < .05$) and marginally significant ($p < .10$) effects of group on percent clustering and switching data. Graphs plot data prior to centering.

