APT-II training in CADASIL: Can a Behavioral Treatment Build Cognitive Reserve?

CADASIL, or *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencoephalopathy*, is a genetic disorder with an estimated prevalence of 1.98 to 4.14 per 100,000 adults (Chabriat & Bousser, 2007). It is characterized by an autosomal-dominant mutation in the *NOTCH3* gene, causing progressive degeneration of vascular smooth muscle cells. By the fourth or fifth decade, repeated small-vessel ischemic events predominate, often leading to classic lacunar syndrome, followed by stepwise deterioration in cognitive function and "pure" subcortical vascular dementia (VaD) (Lesnik-Oberstein & Haan, 2004). The cognitive symptoms reported most often in the earlier stages of CADASIL affect primarily attention, executive function and processing speed, suggesting dysfunction in the frontal cortical-subcortical networks (Chabriat & Bousser, 2007). Most affected individuals demonstrate marked cognitive decline after age 50 years and a detectable dementia soon after age 60 years.

At present, there is no known evidence-based treatment for CADASIL (Rio-Espinola et al., 2009). A possible and relatively unexplored option might parallel the behavioral interventions piloted in mild cognitive impairment (MCI), which similarly involves insidious cognitive decline with no known treatment to reverse the symptomology. A powerful predictor of the conversion (or lack thereof) from MCI to AD/dementia is *cognitive reserve*, i.e., the brain's ability to respond to increased demands in terms of either task complexity per se, or in the face of brain damage (Stern, 2003). It has been suggested that individuals with high cognitive reserve, as measured by educational level, occupation, or neuropsychological test scores, demonstrate a significantly decreased risk of developing dementia. Thus, researchers have begun to explore whether it is possible to *induce* increased cognitive reserve to forestall a dementia diagnosis; for example, via complex cognitive training (e.g., Stern, 2006).

One commercially available program designed for complex cognitive training is Attention Process Training-II (APT-II, Sohlberg et al., 1994), which is the upper extension of Attention Process Training (APT, Sohlberg & Mateer, 1986). APT and APT-II are designed to address deficits in attentional processing, including difficulties coping with distraction, reduced mental control, and shifting attention. The treatment itself is based on the stimulation model of therapy, in which it is assumed that providing systematic opportunities for practicing certain skills will result in improvement in those cognitive or linguistic abilities. APT and APT-II have been extensively evaluated for treating cognition in the TBI population, with positive results (Palmese & Raskin, 2000; Sohlberg et al., 2003).

If increasing cognitive reserve is possible via intensive training for healthy individuals and for individuals with MCI, and if such increased reserve is truly protective against the development of dementia, it follows that this might also be a viable behavioral treatment option for individuals with CADASIL, who demonstrate cognitive deficits early in the disease process and appear to progress uniformly to dementia in time. Furthermore, given the prevalence of attention problems in individuals in the early stages of CADASIL/VaD, APT and APT-II present an excellent context for cognitive training.

The purpose of this study was to test whether a complex training program like the APT-II can increase cognitive function (as measured by attention, memory, executive function, and everyday activities) in an individual with a history of multiple small-vessel ischemic infarctions and probable CADASIL. In the short term, it was hypothesized that the training program would

enhance related cognitive abilities on tests of attention, memory, and executive function. It was further hypothesized that these improvements would be maintained over an extended period of time (i.e., 12-24 months), demonstrating the likelihood of affecting cognitive reserve.

Methods

Participant

A single-subject, multiple-baseline across behaviors design was used to examine the effects of modified APT-II to address cognitive deficits in a 58-year-old male, SB (initials changed) with a history of multiple small-vessel ischemic infarcts and probable CADASIL.

Following IRB approval and informed consent, SB completed an initial test battery examining attention, memory, language, and executive function skills. Consistent with early-stage CADASIL/VaD, SB demonstrated mild, high-level cognitive deficits characterized primarily by slowed processing, attentional and executive dysfunction (Table 1).

Treatment Protocol

SB received cognitive treatment for 90 min. twice-weekly sessions, with an additional 60 min. per day of home practice required, over a period of 10 weeks. Note that this level of intensity well eclipses that suggested in the APT-II manual, consistent with recent emphases on the importance of intensive therapy for generating maximal neural change (Raymer et al., 2008).

The first half of each treatment session followed the hierarchy of attention training tasks laid out in the APT-II manual. Following Sinotte & Coelho (2007), the initial starting point was determined by performance on the TEA, and 80% accurate performance over two consecutive trials was required to progress to the next treatment activity. The second half of each treatment session included strategy training activities (e.g., verbal mediation, rehearsal, anticipation of task demands, self-pacing) following recommendations of Cicerone (2002) and Murray et al. (2006).).

Probes

SB completed auditory and visual attention probes at the beginning of every other treatment session. The auditory attention probe consisted of the Staggered Spondaic Word test (SSW; Katz, 1962), a measure of central auditory function that reflects attention and short-term/working memory (Keller et al., 2006; Riccio et al., 1996). It consists of 10 trials in which four words are presented via headphones in a staggered manner, with dichotic presentation (overlap) of the second and third words. The participant's task is to repeat all four words in order. The primary test measure is percent correct.

The visual attention probe consisted of an experimental version of the n-back task (Kirchner, 1958). The n-back is a continuous performance task in which participants are required to monitor a stream of stimuli for one that matches the stimulus occurring "n" places back in the sequence (Figure 1). SB completed a 2-back task using pictured object stimuli. The primary test measure was "Pr", i.e., accuracy (hit rate) with subtraction of false alarm rate.

Exposure probes, in which new stimuli replaced the SSW and n-back probe stimuli, were created to account for potential practice effects. SB completed the exposure probes at baseline and post-treatment sessions only.

Results

Within Treatment Performance

SB progressed steadily through the modified APT-II program and was able to reach criterion (80% accuracy x 2 per task) with concurrent strategy training and occasional task modification (e.g., slower presentation rate).

Pre- and post-treatment testing

Gains were noted in subtests measuring complex attentional skills, most notably alternating attention (Table 1). SB reported significantly improved functional outcomes (Table 2).

Probe Performance

Baseline stability was unable to be achieved; therefore probe results must be interpreted with caution. Visual inspection shows improved performance over time across both visual (ES = 2.2) and auditory (ES = .55) treatment probes, and in the visual (ES = 5.7) but not auditory exposure probes (Figure 2). Long-term follow-up data will allow for analysis according to reliable change indices (RCI; following Murray et al., 2006).

Conclusions

While results can be cautiously interpreted as providing support for direct attention training in VaD/MCI to improve both impairment-level and functional outcomes, it is likely that the positive outcomes obtained, and SB's perception of generalization of these outcomes to everyday functioning, reflect the strategy training component of therapy, consistent with previous executive training protocols (Cicerone, 2002) and with recommendations for cognitive training in MCI and early AD (Clare et al., 2009).

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Table 1. Selected Pre- and Post- Treatment DKEFS Subtest Scores

Subtest [A]	**Pre-treatment**	**Post-treatment**
Trails:		
Condition 4: Number-letter switching	5[C]	12
Contrast scaled score: Combined number/letter vs. Switching	2[C]	N/A (0)
Fluency: Verbal		
Letter Fluency	8	8
Category Fluency	12	7[B]
Category Switching: Total Correct Responses	6[B]	8
Category Switching: Switching Accuracy	7[B]	9
Letter vs. Category Contrast	6[B]	N/A (-1)
Switching vs. Fluency Contrast	4[C]	9
Color-Word Interference (Stroop)		
Color Naming	10	10
Word Reading	10	9
Inhibition	13	13
Inhibition/Switching	8	12
Completion Times	10	10
Inhibition vs. Color Naming Contrast	13	13
Inhibition/Switching vs. Inhibition Contrast	4[C]	9

Note: [A] Mean = 10, SD = 3; [B]Subtests on which SB scored ≥ 1 SD below the mean; [C]Subtests on which SB scored ≥ 2 SDs below the mean

Table 2: Selected pre- and post-treatment responses to the APT-II questionnaire

Question	**Response Pre-Treatment**	**Response Post-Treatment**
1. Seem to lack mental energy to do activities	Sometimes (1-3x/week)	On occasion (<1/week)
2. Am slow to respond when asked a question or participating in conversations	Sometimes	On occasion
3. Can't keep mind on activity or thought because mind keeps wandering.	Sometimes	On occasion
4. Can only concentrate for very short periods of time	Sometimes	On occasion
5. Miss details or make mistakes because level of concentration decreased	Frequently	On occasion
6. Easily get off track if other people milling about nearby	Frequently	Not a problem
7. Easily distracted by surrounding noise	All the time	Sometimes (1-3x/week)
8. Trouble paying attention to conversation if more than one other person	All the time	On occasion
9. Easily lose place if task or thinking is interrupted	Frequently	On occasion
10. Easily overwhelmed if task has several components	Frequently	On occasion
11. Difficult to pay attention to more than one thing at a time	Frequently	Not a problem
Individualized attention problem list: Describe attention breakdown:	I cannot concentrate when I am meeting with someone in my office with the door open and noise is coming from the hallway. I sometimes have difficulty with teaching children with lots of activity going on: Easily distracted (lose train of thought). Difficulty hearing on the telephone with other noise on the phone or nearby (miscommunication, frustration).	When eating and meeting in a restaurant it is sometimes hard for me to hear and pay attention (I move to a quieter area).

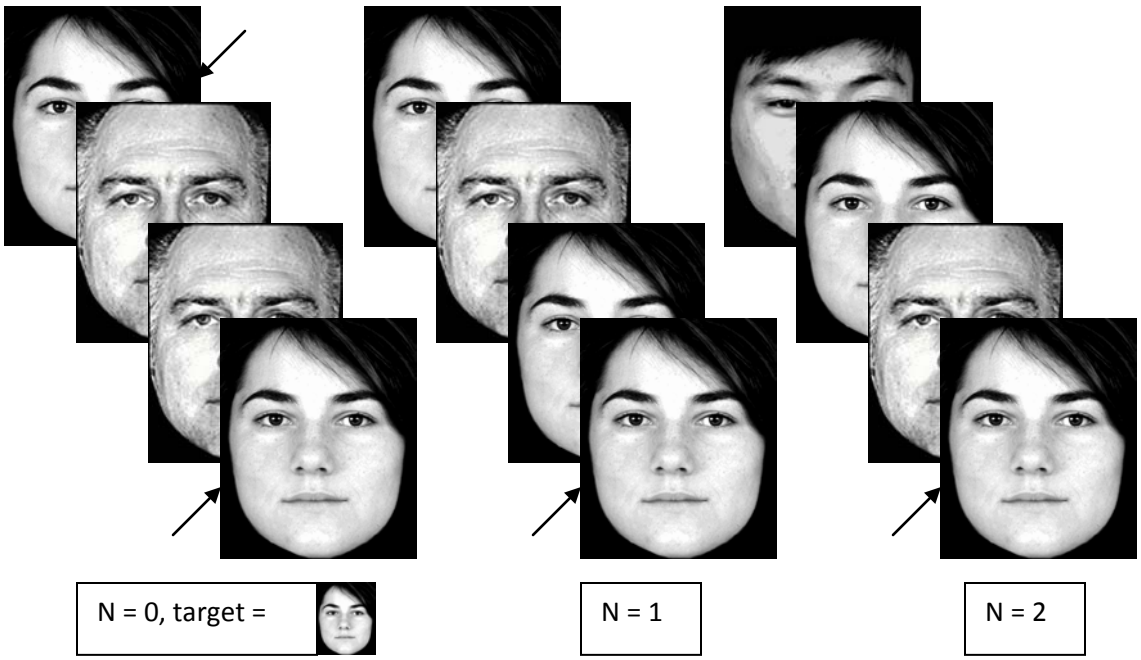

Figure 1. Schematic representation of the n-back tasks (face stimuli; Ekman & Frieson, 1976) at the 0, 1-, and 2-back levels. At the 0-back level, participants decide whether each picture matches a pre-specified target. At the 1- and 2-back levels, participants decide whether each picture matches one that occurred either one or two back in the sequence, respectively. Arrows denote hits.

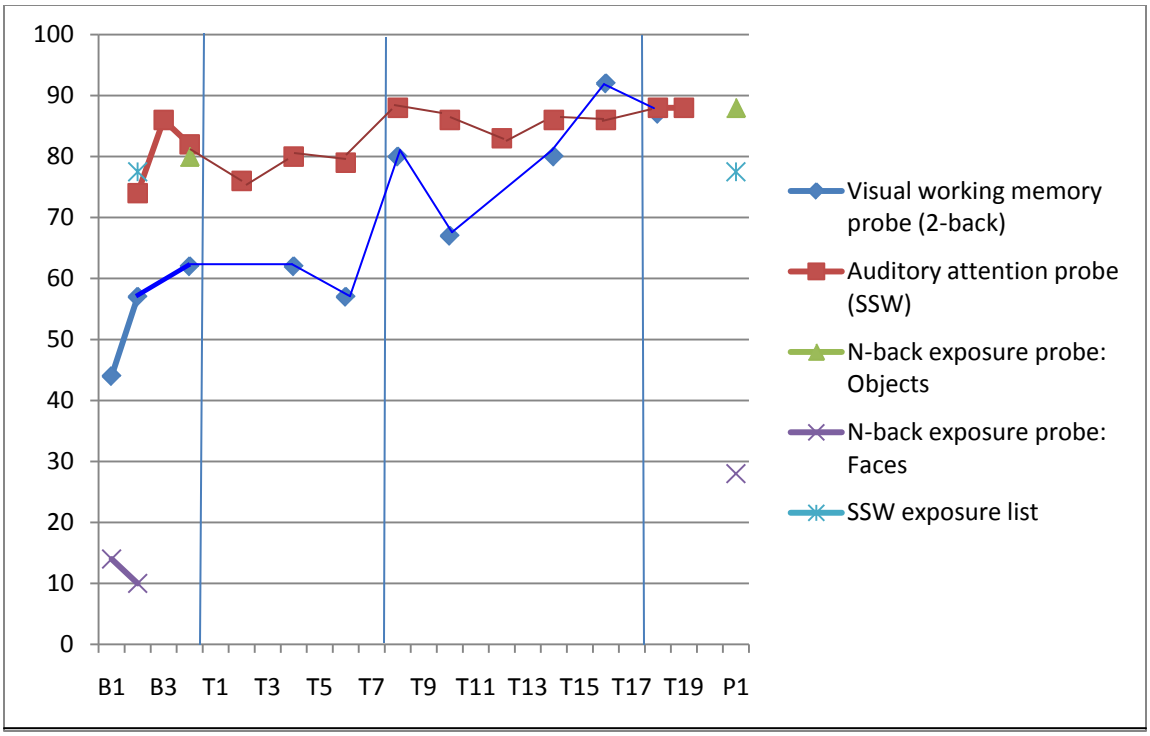

Figure 2. Visual (n-back) and auditory (SSW) attention probes across baseline (B1-B4), treatment (T1-T20; selective attention (T1-T7), alternating attention (T8-T16), divided attention (T17-T20)), and post-treatment conditions (P1). Note the two primary probe sets (visual and auditory) as well as the three exposure sets (two n-back and one SSW).