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EXECUTIVE DEFICITS IN AMYOTROPHIC LATERAL SCLEROSIS: EXAMINING THE CONSEQUENCES OF SELF-REGULATORY IMPAIRMENT ON QUALITY OF LIFE

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Abstract of Dissertation

Abbey R. Roach

The Graduate School
University of Kentucky
2010

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ABSTRACT OF DISSERTATION

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A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By
Abbey R. Roach

Lexington, Kentucky

Director: Suzanne C. Segerstrom, Ph. D., Professor of Clinical Psychology

Lexington, Kentucky

2010

ABSTRACT OF DISSERTATION

EXECUTIVE DEFICITS IN AMYOTROPHIC LATERAL SCLEROSIS: EXAMINING THE CONSEQUENCES OF SELF-REGULATORY IMPAIRMENT ON QUALITY OF LIFE

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that attacks the motor system and contributes to a range of cognitive and behavioral impairments (e.g., behavioral and emotional disinhibition, planning and problem solving difficulties, impulsivity, attention, and personality change). This executive dysfunction may contribute to self-regulatory impairment across several domains, including cognitive skills, thought processes, emotion regulation, interpersonal skills, and physiology, that may be crucial to the quality of life (QOL), or well being, of patients and their caregivers. Given the relentless course and prognosis of ALS, palliative treatments for ALS should target the full range of self-regulatory deficits. Thirty-seven patient-caregiver pairs completed questionnaires regarding the patients' ability to regulate emotions, social behavior, and thought patterns. Patients also completed neuropsychological measures of executive functions and provided measures of glycosylated hemoglobin (A1c) and heart rate variability (HRV). Results suggest that SR and EF deficits exist on a continuum in ALS, such that some patients evidence adequate or superior ability to self-regulate while others evidence deficits. Patient- caregiver agreement about patients' self-regulatory capacity across domains was generally weak to moderate. Patients perceived themselves to have less capacity for global regulation than caregivers perceived them to have, patients perceived less dyadic cohesion than caregivers, and patients perceived themselves to ruminate more than caregivers indicated. Overall, caregivers tended to perceive a more pervasive pattern of deficits compared to patients. Additionally, measures of SR and EF were not strongly inter-correlated in general, challenging the idea that SR in different domains depends on a common resource. Accordingly, correlations among measures of theoretically similar constructs (i.e., EF and SR) were small to moderate in magnitude and non-significant. With regard to physiological functioning, when patients had better regulated glucose (A1c), patients and caregivers perceived better global regulation. A similar pattern emerged with patient ratings, with higher baseline HRV linked to less emotional lability. Last, mixed results were obtained when predicting patient and caregiver QOL. Less rumination, less dyadic cohesion and more social anxiety were associated with higher QOL for patients. Caregivers' QOL was not significantly related to their perceptions of patients' self-regulatory capacity in any area.

Keywords: Amyotropic Lateral Sclerosis (ALS), Self-Regulation, Executive Functioning, Quality of Life, Heart Rate Variability.

                                                  Abbey R. Roach
                                                Student's Signature

                                                March 31, 2010
                                                    Date

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DISSERTATION

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ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter One

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive and invariably fatal

neurodegenerative disease with few options for treatment and no cure. Most people with ALS

die within 5 years of the onset of a host of motor symptoms including muscle atrophy and

cramps, spasticity, fasciculations, progressive motor weakness, and eventual paralysis. The

effects of ALS, however, are often not contained to the motor system, and may include some

degree of cognitive and behavioral impairment typically believed to be associated with frontal

lobe dysfunction, such as behavioral and emotional disinhibition, planning and problem

solving difficulties, impulsivity, attention, and personality change (Neary, Snowden, Mann,

Northern, Goulding, & Macdermott, 1990). However, rapid physical deterioration may

overshadow ALS patients' cognitive deficits (Irwin, Lippa, & Swearer, 2007), which may

range from subtle to severe. Furthermore, these deficits may be related to problematic

behaviors and thoughts across domains important to functioning. Consequently, there is a

need to clarify the prevalence and pattern of cognitive and behavioral deficits in ALS, which

have a sizeable impact not only on the patients' physical health and survival, but also on their

sense of well being, or quality of life (QOL), as they approach the end of life.

What is ALS?

Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disease affecting

approximately 30,000 people in the United States (ALS Association, 2004) that involves the

progressive degeneration of upper and lower motor neurons, leading to muscle weakening and

wasting, eventual paralysis, and death (commonly from respiratory failure) (NINDS, 2003).

ALS comprises one major subtype of Motor Neuron Diseases (MND), which encompasses the

group of neurological disorders involving disrupted communication between nerve cells in the

brain and those in the spinal cord. Although ALS is synonymous with MND in North America

and continental Europe (Bak, O'Donovan, Xuereb, Boniface, & Hodges, 2001; Goldstein,

Atkins, & Leigh, 2002; NINDS, 2009), there are various subtypes of MND, based primarily on

the site of motor neuron degeneration. In particular, Primary Lateral Sclerosis (PLS), which is

considered a variant of ALS, initially affects only upper motor neurons and typically has a

slower rate of progression (NINDS, 2009). Much research on MND however, encompasses

individuals with MND in general, or does not specify the subtype(s) included in the sample.

In fact, some experts suggest that ALS and PLS could be 2 points on a continuum of MND,

and not distinct disorders (Tartaglia, Rowe, Findlater, Orange, Grace, & Strong, 2007).

Therefore, throughout this paper, the term ALS will be inclusive of other subtypes of MND

(i.e., PLS).

No cure exists for ALS, and treatment options are similarly limited for both ALS and

PLS. Although ALS has a more relentless course than PLS and is often fatal, up to 10% of

people with ALS may survive up to 10 years after symptom onset (ALS Association, 2004).

On the other hand, PLS is not fatal and advances much slower (NINDS, 2009). This

highlights the need to examine the complete scope and trajectory of the disease course as well

as psychological and personality factors that may influence patients' treatment compliance,

survival, and psychological well being, as well as that of the person providing their care.

Cognitive Functioning in ALS

Although originally conceptualized as a purely motor disease, ALS is increasingly

recognized as a multi-system disorder (Strong, 2001, 2008; Strong & Rosenfeld, 2003) that is

"recognized to include cognitive impairment" (Wilson, Grace, Munoz, He, & Strong, 2001).

However, how to best conceptualize the range and scope of extra-motor deficits in ALS

remains a topic of debate. It is clear that not all people with ALS have severe cognitive and

behavioral impairment, and thus it is increasingly believed that people with ALS "with and without cognitive impairment represent a disease continuum" (Ringholz, Appel, Bradshaw, Cooke, Mosnik, & Schulz, 2005, p. 589; Yang, Sopper, Leystra-Lantz, & Strong, 2003). Evidence that up to 50% of ALS patients exhibit mild cognitive impairment (Lomen-Hoerth, Murphy, Lagmore, Kramer, Olney, & Miller, 2003; Massman, Sims, Cooke, Haverkamp, & Appel, 1996; Ringholz et al., 2005) and approximately 15% of people with ALS meet criteria for frontotemporal dementia[1] (FTD; Barson, Kinsella, Ong, & Mathers, 2000; Neary, Snowden, & Mann, 2000) suggests that cognitive decline may be a progressive feature of ALS (Ringholz et al., 2005), such that some degree of cognitive problems precedes more obvious motor impairments (Robinson, Lacey, Grugan, Glosser, Grossman, & McCluskey, 2006; Schriber et al., 2005), making the issue of cognitive impairment in ALS potentially relevant to all people with ALS. Therefore, limiting the scope of interest to extensive impairment is dangerous for people with ALS who have less pronounced or sub-threshold deficits in domains critical to their functioning that affect treatment compliance, quality of life, and survival (Irwin et al., 2007; Olney et al., 2005).

While the prevalence of extra-motor impairment in ALS remains an area of debate, the most consistent pattern of cognitive and behavioral deficits target language skills (e.g., verbal fluency) and executive functions (EF) as measured by tasks of planning and problem solving abilities, inhibition, attention, cognitive flexibility, and verbal and non-verbal fluency (Abrahams, Leigh, Harvey, Vythelingum, Grise, & Goldstein, 2000; David & Gillum, 1986;

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[1] FTD involves frontal and temporal lobe atrophy and is characterized by pathological changes in language, perception, motor skills, memory, planning, behavior, and performance quality (Neary & Snowden, 1996).

Frank, Haas, Heinze, Stark, & Munte, 1997; Irwin et al., 2007; Massman et al., 1996; Strong, Grace, Orange, Leeper, Menon, & Aere, 1999; Talbot, Goulding, Lloyd, Snowden, Neary, & Testa, 1995).

Executive Functions

Executive functions (EF) refer to a "wide range of cognitive processes and behavioral competencies which include verbal reasoning, problem-solving, planning, sequencing, the ability to sustain attention, resistance to interference, utilization of feedback, multi-tasking, cognitive flexibility, and the ability to deal with novelty" (Chan, Shum, Toulopoulou, & Chen, 2008, p. 201). Although there is general agreement that 'executive functions' is a non-unitary concept (Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999) that enables the "control and regulation of lower-level cognitive processes and goal-directed, future-oriented behavior" (Alvarez & Emory, 2006, p. 17), there is less agreement regarding the best way to decompose 'executive functions' into sub-constructs (e.g., initiating, inhibiting, switching).

Given that "a compelling theory of executive functions" is lacking (Miyake, Freidman, Emerson, Witzki, Howerter, & Wager, 2000, p. 50) and the absence of a gold-standard conceptualization of EF (Aron, 2008), studying EF can be difficult. This theoretical ambiguity likely contributes to another difficulty with research on EF- "the lack of a clear gold standard measure against which putative EF measures can be compared" (Royall et al., 2002, p. 381). First, although 'executive' and 'frontal lobe' tasks are often used interchangeably, "the use of executive function tests as 'frontal lobe indicators' is not warranted by the data" (Alvarez & Emory, 2006, p. 32). While the frontal lobes may participate in functions deemed as 'executive', other brain regions are also important to EF. Second, most evidence suggests that measures of EF have low reliability and low intercorrelations (Alvarez & Emory, 2006; Miyake et al., 2000), which is not surprising if measures of 'sub-constructs' are compared.

4

Thus, the heterogeneous nature of EF suggests that quantifying EF using measures conceptualized at a higher level (as opposed to sub-construct level) might be unhelpful.

One useful model of EF is Damasio's (1995) somatic marker hypothesis, which distinguishes between logically-driven ("cold" functions) and emotionally-driven ("hot" functions) decision making (Bechara, Damasio, & Damasio, 2000). Specifically, the "cold" component of EF enables activities such as planning, sequencing, utilization of feedback, multi-tasking, cognitive flexibility that are incorporated in traditional conceptualizations of EF. Conversely, the "hot" components of EF involve emotional arousal, beliefs, and "regulation of one's own social behavior" (Chan et al., 2008, p. 201). Thus, emotionally triggered decision making is considered a "hot" function. It is likely that these "hot" and cool" functions are mediated by related, but different regions of the brain (Bechara et al., 2000; Owen, McMillan, Laird, & Bullmore, 2005). Evidence for this hypothesis is largely derived from the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Andersen, 1994), a task that assesses real-life decision making with regard to reward, punishment, and uncertainty. The IGT is considered more "ecologically valid" than traditional measures of EF (e.g., Wisconsin Card Sorting Test), as it adopts a more contextual and behavioral approach to examining EF in settings representative of "real-world" situations (Alvarez & Emory, 2006; Manchester, Priestly, & Jackson, 2004; Ready, Stierman, & Paulsen, 2001). Thus, it is thought to better reflect "the nature of impaired executive functioning in everyday life" than standard neuropsychological tests that automatically control the environment (e.g., noise, distractions), direct behavior (e.g., prompting and stopping behavior), and limit affective arousal (Alvarez & Emory, 2006, p.1068; Manchester et al., 2004).

Executive Functions and Self-Regulation

There is general agreement, however, that EF broadly defined "control and regulate thought and action" (Friedman, Miyake, Corley, Young, DeFries, & Hewitt, 2006, p. 172), "enable us to formulate goals and plans" (Aron, 2007, p. 124), and are important to "independent and responsible social behavior" (Lezak, 1993, p. 30). Likewise, self-regulation (SR) is "the ability to control or override one's thoughts, emotions, urges, and behavior" and refers to processes that enable adaptive behavior and "flexibility necessary for…goal attainment" (Galliot et al., 2007, p. 325).

Both of these control resources are limited and can be exhausted, resulting in problems in controlling and regulating behavior and difficulty functioning in everyday life (Baumeister, Bratslavsky, Muraven, & Tice, 1998; Galliot et al., 2007; Marios & Ivanhoff, 2005; Miyake et al., 2000; Schmeichel, 2007; Vohs, Baumeister, & Ciarocco, 2005). On the other hand, both can also be strengthened or enhanced through practice (Davidson, Zacks, & Williams, 2003; Muraven, Baumeister, & Tice, 1999; Oaten & Cheng, 2006). Successful SR and executive control have positive outcomes (e.g., more effective coping skills, superior academic performance, less susceptibility to substance abuse, and reduced aggression; Galliot et al., 2007).

Although there are conceptual similarities between EF and SR (Kaplan & Brown, 2010), they are often measured differently. Specifically, EF is relatively content-free, often referring to unpracticed ability to perform cognitive operations (as measured by standard neuropsychological tests). SR, on the other hand, is a content-rich, practiced function that gains meaning when interpreted within the context of real-life situations. Thus, EF likely contributes to the ability to self-regulate in various situations. Accordingly, Schmeichel (2007,

p. 251) suggests that "depleted self-regulatory resources may more precisely be considered instances of reduced resources for executive control".

Self-Regulatory Challenges in ALS

Although standard neuropsychological tests of EF may highlight cognitive deficits in ALS (e.g., FTD), there may be evidence of impairment in equally important areas, such as emotion regulation, social regulation, and the regulation of thought processes.

Emotional

According to Gross (1998), emotion regulation "refers to the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions" (p. 275). Thus, emotion regulation is conceptualized as a self-regulatory capacity that "involves the initiation of new, or the alteration of ongoing, emotional response through the act of regulatory processes" (Oschner & Gross, 2005, p. 242). Successful SR of emotions may depend on executive control, which is supported by evidence that the brain circuitry involved in the control of emotions overlaps with that involved in cognitive tasks measuring EF (Rule, Shimamura, & Knight, 2002; Taylor, Burkland, Eisenberger, Lehman, Hilmert, & Lieberman, 2008). For example, inhibition likely contributes to successful performance on cognitive tasks (e.g., WCST) as well as the regulation of emotional expression.

Emotion regulation is particularly relevant in ALS. Up to half of the people with ALS experience "sudden episodes of emotional display or pathologic laughing and crying (PLC)" (McCullagh, Moore, Gawel, & Feinstein, 1999, p. 43). Even more, ALS patients with PLC performed significantly worse than ALS patients without PLC on the WCST (McCullagh et al., 1999). Mood disturbances (e.g., depression, anxiety) may also be viewed as a failure to regulate emotions. Some research suggests that negative affect is common in people with ALS

(Tedman, Young, & Williams, 1997) with 44% to 75% of patients with ALS having observable depression (Hogg, Goldstein, & Leigh, 1994; Tedman et al., 1997), and up to 42% of patients having anxiety in the medium to high ranges (Wicks, Abrahams, Masi, Hejda-Forde, Leigh, & Goldstein, 2007). However, more recent evidence proposes that people with ALS have minimal or mild symptoms of depression (Gauthier et al., 2007; Kilani et al., 2004; Rabkin et al., 2005). In sum, not all people with ALS exhibit grossly inappropriate emotional responses, which suggests that self-regulatory capacity to regulate one's behavior and emotions may be an individual difference. Hence, examining the range of these impairments as well as their impact on patient and caregiver well being is important.

Social

Social interactions, including benign interactions such as coordinating interpersonal efforts (e.g., to solve a problem; Finkel, Campbell, Brunell, Dalton, Scarbeck, & Chartrand, 2006), rely on self-regulatory capacity. Furthermore, reduced self-regulatory resources result in passivity in social interactions. Other research indicates that low-anxious, socially active people can expend the resources needed to overcome this passivity, but socially anxious people do not have these self-regulatory resources upon which to draw (Baumeister, Gailliot, DeWall, & Oaten, 2006).

Social relationships and support, albeit linked to high QOL in people with ALS (Simmons, Bremer, Robbins, Walsh, & Fischer, 2000), may require a great deal of SR to maintain. First, problems with communication (e.g., dysarthria; Strong, Grace, Orange, & Leeper, 1996), reduced verbal output, and eventual mutism (Bak et al., 2001) may limit social interactions. Next, behaving in a socially appropriate way requires reasonably intact cognitive functions (e.g., attention, memory) and emotional control. In fact, caregivers report that some patients "do not seem to understand or care about the feelings of others" (Grossman, Woolley-

8

Levine, Bradley, & Miller, 2007, p. 56). Altered social conduct in ALS is sometimes

characterized by over-activity and unrestrained behaviors (e.g., "inappropriate disrobing,

touching of staff, and/or inappropriate jokes"; Lomen-Hoerth et al., 2003, p. 1096) and

sometimes characterized by apathy and lack of drive or initiative (Neary & Snowden, 1996). It

seems most reasonable that this alteration in social conduct occurs progressively in some

people with ALS, such that symptoms exist on a continuum that may be related or unrelated to

the physical disease course.

Thoughts

Cognitive inflexibility, or perseveration, may be among the cognitive deficits observed

in ALS. Perseveration, described as "repetitive, abstract, involuntary, and represent[ing] a

failure of neuronal processes" (Thayer & Lane, 2002, p. 686), is characterized by an inability

to adaptively adjust one's thoughts. This cognitive inflexibility makes it difficult to change the

way one thinks and feels, which may interfere with one's ability to cope with challenges or

achieve goals. Even more, perseveration is associated with rumination (Davis & Nolen-

Hoeksema, 2000). Ruminations are "perseverating self-focused thoughts" (Hertel, 1998, p.

166) that can interfere with a person's ability to inhibit thoughts, generate alternative ways of

thinking about a situation, or switch the focus of one's attention (Davis & Nolen-Hoeksema,

2000; Watkins & Brown, 2002). One study reported that nearly half of patients with ALS

endorsed ruminating as a coping strategy and that higher rumination scores were related to

higher depression (Hecht et al., 2002). Despite the negative outcomes of perseverative

thinking, patients perceive rumination as a helpful strategy (Earll, Johnston, & Mitchell, 1993).

This may describe a more general tendency of people with ALS to engage in these

perseverative thought processes, and may account for the lack of regulatory effort expended to

overcome this tendency.

Repetitive thought is not always harmful (Segerstrom, Stanton, Alden, & Shortridge, 2003), but several factors may make worry an unhelpful problem solving strategy for patients with ALS. First, patients' decision making may have little impact on their ultimate disease trajectory. Second, patients' prognosis is generally known to be poor, which may make certain forms of worry more maladaptive (Wilson, Centerbar, Kermer, & Gilbert, 2005). Last, if patients' self-regulatory resources are taxed or depleted, they might not only be more prone to perseverative thoughts, but have less strength to engage in alternative thought processes. This highlights the importance of viewing perseverative cognitions along a continuum in relation to self-regulatory resources, such that at a mild or moderate level, perseverative cognitions may be less harmful (or even helpful), but at high levels (i.e., where inhibitory processes are ineffective), the consequences may be greatest.

Physiological Self-Regulation in ALS

Metabolic and autonomic resources may be important components of the capacity for executive control, and may be especially important for people with ALS. First, EF are considered "metabolically expensive" in terms of the amount of glucose required to optimally function (Gailliot, 2008, p. 245). Specifically, low levels of blood glucose and poor glucose tolerance have been linked to impaired performance on tasks involving processes that rely on executive function (i.e., Stroop Test; Benton, Owens, & Parker, 1994; Fairclough & Houston, 2004) as well as SR (e.g., attention, impulsivity, emotion regulation; see Gailliot & Baumeister, 2008 for a review). Furthermore, optimal levels and transport of glucose are linked to increased ability to exert self-control (Huisman, Gucht, Maes, Schroevers, Chatrou, & Haak, 2009) and better performance on cognitive tasks (Gailliot, 2008; Gailliot & Baumeister, 2008). Thus, glucose is a resource that appears to be important to a person's ability to self-regulate in various domains, including EF.

Given that glucose enables SR in multiple domains, glucose levels and tolerance may be especially important for people with ALS, who may be especially prone to self-regulatory deficits. Indeed, there is evidence of impaired glucose transport in the cerebral cortex in some rat models of ALS (Guo, Kindy, Kruman, & Mattson, 2000). Research has also revealed a link between mild frontal dysfunction and reduced glucose metabolism in the cortex and subcortical structures of ALS patients (Ludolph et al., 1992). Low glucose levels and impaired glucose transport in people with ALS may partially account for impairments in self-regulatory and executive abilities, which are expensive in terms of glucose. Specifically, for people with ALS who have low glucose levels and/or impaired glucose transport (e.g., poor glucose tolerance), executive impairments may be most pronounced. On the other hand, adequate levels of glucose and optimal transport may enable people with ALS to self-regulate more successfully across domains.

Another potentially important physiological correlate of self-regulatory capacity is heart rate variability (HRV), an autonomic measure of beat to beat variations in heart rate that "reflects the ability to allocate and maintain attention, which are crucial to the control of emotion and performance" (Demaree, Pu, Robinson, Schmeichel, & Everhart, 2006, p. 162). HRV, like glucose, is associated with prefrontal activity and SR (e.g., inhibition, cognitive flexibility, delayed response). Specifically, low resting HRV may correlate with decreased prefrontal activation, impaired EF, disrupted emotion modulation (i.e., enhanced/prolonged threat response), and perseverative thoughts (Brosschot, Thayer, & Gerin, 2006; Thayer, 2007). Low resting HRV also predicts less persistence on tasks requiring self-regulatory effort (Segerstrom & Solberg Nes, 2007). Additionally, elevated heart rate (HR) and decreased HRV were independently associated with stressful events and worry (particularly worry about future events), when controlling for personality, mood, and demographic factors (Pieper, Brosschot,

11

Van der Leeden, & Thayer, 2007). However, increased emotional display and impaired regulation of negative affect (e.g., anxiety, depression, hostility) have also been related to "reduced cardiac vagal control" (i.e., HRV) (Carney, Freedland, & Stein, 2000; Demaree & Everhart, 2004; Demaree, Pu, Robinson, Schmeichel, & Everhart, 2004; Friedman & Thayer, 1998a, 1998b).

There is converging evidence of impaired autonomic functions in ALS. In fact, some suggest that "deterioration of sympathetic function is part of the disease process" (Oey, Vos, Wieneke, Wokke, Blakestijn, & Karemaker, 2002, p. 403). ALS patients have "blunted vagal control" (i.e., decreased HRV; Pisano, Miscio, Mazzuero, Lanfranchi, Colombo, & Pinell, 1995). Interestingly, this sympathovagal imbalance is not correlated with disease severity. Not only may it be difficult to predict which people with ALS will suffer these cardiovascular deficits, those patients with more salient or obvious motor impairments may sometimes be more equipped to persist in the face of self-regulatory challenges than seemingly "intact" patients, further highlighting the importance of examining the full range of deficits in ALS, from sub-threshold to severe.

It is possible that the metabolic demands and autonomic responses involved in exerting executive control and enabling SR are related. In fact, Brook and Julius (2000) propose that autonomic imbalance is related to a range of cardiovascular abnormalities (including metabolic). Decreased HRV has been linked to conditions involving impaired glucose metabolism (e.g., diabetes; Schroeder et al., 2005; Ziegler, Dannehl, Volksw, Muhlen, Spuler, & Gries, 1992). Taken together, these data imply that SR and EF are overlapping and related constructs that rely on a similar energy resource (e.g., glucose) and that have at least one common autonomic marker (e.g., HRV). These cardiovascular and metabolic factors associated with SR may be particularly important for people with ALS. It could be true that

the relationships between physiological factors (e.g., HRV, glucose) and SR are interactive. Self-regulatory fatigue may tax metabolic energy resources, making them less available for subsequent efforts at executive control, thereby resulting in the range of deficits noted in some individuals with ALS. On the other hand, people with ALS may have impaired metabolic and cardiovascular functions that limit the success of their attempts to self-regulate, thereby resulting in the range of self-regulatory deficits in ALS.

Self-Regulatory Deficits and Well-being

Deficits across psychological and physical domains may not only share a common mechanism (i.e., SR), but may also be interactive. For example, cognitive deficits (e.g., EF and social cognition) can lead to altered interpersonal and socio-emotional functioning (Zimmerman, Eslinger, Simmons, & Barrett, 2007). Refined assessment of self-regulatory deficits across multiple domains may improve the prognosis of patients with ALS- not pertaining to their physical health, but to their well being or quality of life (QOL). Specifically, well being in a variety of domains (e.g., social, psychological, physical, existential) is important to overall QOL, while disease progression or loss of physical function appear to be less important to QOL (Averill, Kasarskis, & Segerstrom, 2007; Roach, Averill, Segerstrom, & Kasarskis, 2009). In fact, when asked about the determinants of their own QOL, people with ALS refer to the importance of "psychological and existential issues, and support factors" rather than physical function (Simmons et al., 2000, p. 391). In one group of people with ALS, decreased social support was the best predictor of psychological wellbeing and self-esteem (Goldstein, Atkins, Landau, Brown, & Leigh, 2006). Evidence that higher QOL results in longer survival (Johnston, Earll, Giles, McClenahan, Stevens, & Morrison, 1999; McDonald, Widenfeld, Hillel, Carpenter, & Walte, 1994) suggests that QOL is a "critically important endpoint in ALS" (Hardiman, Hickey, & O'Donerty, 2004, p. 233) and

that it should be a major focus of clinical care and interventions (e.g., Chio et al., 2004, 2005; Mitsumoto & DelBene, 2000).

Reduced ability to self-regulate could result from decreased baseline capacity or from depleted executive resources due to the progressive and demanding disease course of ALS. Regardless of the cause, an inability to adaptively adjust and pursue one's goals (explicit or implicit) ultimately influences the well being of people with ALS. Thus, examining SR in ALS may enhance clinical interventions that tend to more narrowly focus on patients' most extreme (often motor) deficits.

Attending to the needs and well being of those providing the care for people with ALS is equally crucial, given that caregiver mental status influences patients' physical, psychological and existential wellbeing (Rabkin, Wagner, & Del Bene, 2000). Some even suggest that interventions to improve patients' QOL should largely focus on caregivers, who support patients and relieve their distress, and that health care providers should focus on improving the coping skills of caregivers (Chio et al., 2004). Despite evidence that caregiver well being is important to patient well being, caregiving appears to take quite a toll on the QOL of these individuals. Caregivers in one longitudinal study exhibited a significant increase of burden and depression over a 9-month period (Gauthier et al., 2007). Thus, caregivers may be more psychologically vulnerable to patients' disease-related physical deterioration than patients themselves. Given that ALS is a multi-system disorder as described above, factors other than physical disease progression may also be important to caregiver QOL. Specifically, "patient's cognitive functioning is an important factor in determining the level of burden" of caregivers (Chio et al., 2005, p. 781). Thus, examining the range of self-regulatory deficits in ALS has implications for both patients and for those caring for them.

The Current Study

The aims of this study were to test the following hypotheses in patients and caregivers:

1. There will be between-patient variability in EF and self-regulatory capacity. Specifically, examining the distribution of executive and self-regulatory impairments (with regard to emotions, thought processes, and social interactions) in patients will reveal continuous distributions of scores on measures of SR and EF, supporting the idea that deficits exist on a spectrum, rather than being discrete disease entities or classes, such as FTD.

2. Patients' and caregivers' ratings of SR will be positively correlated (Adelman, Albert, Rabkin, Del Bene, Tider, & O'Sullivan, 2004) so that in general, as patients perceive more problems, caregivers also perceive more problems. However, we expect mean-level differences (patients will rate their problems as less severe than caregivers rate their problems) as well as a non-linear relationship between patient and caregiver ratings of SR (as deficits increase, patient and caregiver reports will diverge, possibly because patients aren't able to realistically evaluate their condition; Lezak, 1995) . If patient and caregiver reports are moderately and linearly related, they will be combined into composite scores for SR and EF to test subsequent hypotheses.

3. The third aim of this study is to establish the construct validity of EF and SR by examining relationships among reports of SR in various domains (e.g., global regulation, social regulation, emotional regulation, regulation of thought processes) and executive functions in "hot" and "cool" domains. Moderate correlations ($r \geq .30$) between different measures of EF/SR and weaker relationships ($r \leq .10$) with divergent measures would support the use of composite EF/SR indices.

4. EF will contribute to self-regulatory capacity, even when controlling for potentially confounding variables (e.g., intelligence, ventilation status, etc.).

5. SR and EF will correlate with physiological measures of HRV and A1c. Specifically, HRV will be lowest and A1c will be highest in those patients with more self-regulatory and executive deficits.

6. Patients' self-regulatory capacity, executive functioning, and physiological factors (i.e., baseline HRV and A1c) will contribute to QOL. Specifically, more self-regulatory and executive impairment, lower baseline HRV, and higher A1c are expected to be associated with poorer QOL. This may be especially true for caregivers.

Chapter Two

Method

Participants

Thirty-seven patients with motor neuron disease (31 ALS, 6 PLS) and their primary

caregivers were enrolled in the study. This sample provided adequate power (.90) to detect a

large effect ($r = .50$) of SR on EF. Demographic characteristics of the sample are provided in

Table 1. The sample was representative of the population of individuals diagnosed with motor

neuron disease with regard to gender and age (NINDS, 2003).

Thirty-seven caregivers were recruited to participate in this study. However,

demographic data were only available for 36 caregivers as 1 caregiver did not complete the

questionnaires. In general, men were more likely to be cared for by an opposite-gendered

caregiver and females were more likely to have a same-sex caregiver.

Procedure

Participants were recruited for the study though ALS clinics at the University of

Kentucky and Cardinal Hill Rehabilitation Hospital in Lexington, Kentucky. A letter was

mailed to all ALS clinic patients informing them about the study. Patients were encouraged to

respond (via an enclosed response card or via their physician during their clinic visit) if they

were interested in participating. A research assistant followed up with each patient either in

person or by phone to determine eligibility.

To be eligible for participation, the following criteria were met: diagnosis of ALS

(according to the El Escorial Criteria; World Federation of Neurology Research Group on

Motor Neuron Diseases, 1998) or PLS (Pringle, Hudson, Munoz, Kiernan, Brown, & Ebers,

1992), diagnosis greater than 6 months prior to participation, age between 30 and 90 years, no

diagnosis of Type 1 Diabetes, fluency in English, and having a caregiver willing to participate.

Sixty-four patients expressed interest in this study. Fourteen individuals initially expressed interest but declined to participate after hearing more about the study, 6 individuals cancelled their appointments and were not able to reschedule, 2 individuals were diagnosed within the past 6 months, 2 individuals were hospitalized with pneumonia prior to participating, 1 individual was diagnosed with Type 1 Diabetes, and 2 individuals died before participating in the study. Thus, 37 patients provided informed consent to participate in this study.

Most patients were tested at Cardinal Hill Rehabilitation hospital (N=30). However, 7 patients were tested in their home because they were unable to travel to the testing site (e.g., due to mobility problems, lack of/cost of transportation, scheduling conflicts). Upon arriving to the appointment, informed consent was reviewed with participants.   Caregivers were provided a packet of questionnaires to complete in a separate room. Physiological equipment was attached to the patient, and the patient was instructed to sit and relax for 5 minutes to obtain baseline physiological measurements. Upon completion of the 5 minute baseline period, participants completed 2 computerized neuropsychological tests, the physiological leads were removed, and 2 more neuropsychological tests (i.e., booklets) were administered. Questionnaires (assembled in counter-balanced order) were then verbally administered to patients by the principal investigator. Patients responded to each item using a visual scale card provided. Upon completing these questionnaires, a finger prick was administered to obtain a blood sample for measurement of A1c. Patients were offered breaks as needed throughout the testing. The range of time required to complete the protocol was between 2 and 3 ½ hours (Mean= 2.29 hours, SD= .34 hours). Participants were mailed $50 for participating in the study.

Measures

Descriptive Measures

Demographics. Demographic information (e.g., age, gender, ethnicity) was obtained from patients and caregivers (see Table 1). Additionally, patients provided disease-related information (e.g., dates of diagnosis and symptom onset, onset site).

Self-Regulation Measures

Revised Dyadic Adjustment Scale-cohesion scale (RDAS; Busby, Crane, Larson, & Christensen, 1995)*.* This is a 16-item self-report measure of relationship quality developed for married or similar, cohabiting dyads. The revised version of the scale contains 3 subscales (consensus, satisfaction, and cohesion) in addition to the total score. The 4-item cohesion subscale (α=.80) was used in the current study to focus on patients' social SR with the individual providing their care. This subscale is composed of items that are not specific to marital dyads (e.g., "how often do you and your [caregiver] work on a project together?"). Lower scores indicate better relationship cohesion. The internal consistency of this scale in the current sample was .81 for patients and .75 for caregivers.

Brief Fear of Negative Evaluation scale (BFNE; Leary, 1983). This self-report measure of social anxiety (e.g., apprehension about being negatively evaluated, avoiding being evaluated, and expecting the receipt of negative evaluation) consists of 12 items scored on 5-point Likert-type scales. The scale was selected due to evidence that self-regulatory capacity determines whether an individual is successful at overcoming social anxiety, which is shared, to a certain extent, by all individuals (Baumeister et al., 2006). Lower scores on this scale are more adaptive (i.e., indicative of less social anxiety). The internal consistency of this scale in the current sample was .94 for patients and .96 for caregivers' reports of patients.

Center for Neurologic Study- Lability Scale (CNS-LS; Moore, Gresham, Bromberg, Kasarskis, & Smith, 1997)*.* This is a 7-item self-report measure of affective lability in patients with ALS. The scale consists of 2 subscales, labile laughing (4 items) and labile tearfulness (3

items), both of which have acceptable internal consistency (.91 and .89, respectively).

Participants respond on a 5-point Likert scale, with higher scores indicative of more emotional

lability or dysregulation. The internal consistency of this scale in the current sample was .86

for patients and .78 for caregivers' reports of patients.

Rumination Scale (*RS;* Martin, Tesser, & McIntosh, 1993). This was originally a 10-

item self-report measure of conscious, repetitive, persistent, aversive thought that is best

described by a two-factor solution (Segerstrom et al., 2003). The 4-item lack of control over

thoughts/ distractibility scale was used as a measure of ability to regulate one's thought

processes in the current study. However, the internal consistency of this 4-item scale was poor

for both patients and caregivers in the current sample. The deletion of 1 item (i.e., "If I don't

want to think about something, I am able to just stop thinking about it.") from the scale

improved the internal consistency of patients and did not significantly affect that of caregivers,

resulting of alphas of .53 and .62, respectively. Lower scores on this scale represent better

ability to regulate one's thought processes.

Behavioral Rating Inventory of Executive Functions (BRIEF; Roth, Isquith,

& Gioia, 1996). This is a 75-item measure of executive regulation of behavior with self- and

informant-report forms. This inventory consists of nine non-overlapping empirically derived

clinical scales that measure various aspects of executive functioning as applied to daily life

(Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control,

Working Memory, Organization of Materials), that form two broader indexes of behavioral

regulation and meta-cognition. Both the scales and indexes have adequate internal

consistency, ranging from .73-.90 for clinical scales and .93-.96 for indexes on the self-report

form and .80-.93 for clinical scales and .95-.98 for indexes on the informant-report form. This

scale is appropriate to measure a variety of forms of SR, both from the patients' and

caregivers' perspectives. In the current study, several items were deleted to prevent overlap with disease symptoms. Specifically, items that were believed to be overlapping with the physiological disease process involved in ALS or PLS (e.g., "taps fingers or bounces legs", "has trouble sitting still", "lies around the house a lot") were not included in the total score. The total score was used in the current study as a self-reported measure of global regulation with higher scores indicating worse global regulation.

Neuropsychological Measures

Iowa Gambling Task (IGT; Bechara et al., 1994*).* This computer-administered task assesses "real-life" decision making ability in an "ecologically valid" paradigm in accordance with Damasio's (1995) somatic marker hypothesis. Participants are instructed to choose one of four decks (A, B, C, D; 60 cards each) until 100 selections have been made. After each selection, participants receive a reward and/or penalty in play money. The decks have pre-determined rewards and penalties (e.g., Decks A and B have a high rewards and penalties, decks C and D have low rewards and penalties). Additionally, decks A and C have more frequent penalties and decks B and D less frequent penalties. A greater selection of cards from decks A and B (disadvantaged decks) results in a net loss and a greater selection of cards from decks C and D (advantage decks) results in a net gain. The performance measure used in this study was the number of cards picked from advantaged decks minus the number of cards picked from disadvantaged decks. After reversing the direction of this scale, lower scores indicate better "hot" executive function.

Wisconsin Card Sorting Test (WCST; Berg & Grant, 1948*).* This task requires participants to sort response cards (i.e., according to color, shape, and number) according to feedback (i.e., right or wrong) until they have matched six categories or sorted all 128 cards. The sorting rules change after 10 consecutive correct card sorts, requiring participants to

demonstrate cognitive flexibility to shift sets. The performance measure used in the current study was the number of perseverative errors, which represents cognitive inflexibility or failure to shift sets in response to changing demands (Ridderinkhof, Span, van der Molen, 2002). Although there is controversy surrounding the validity of this test as a measure of EF, it is the most frequently used measure of EF and is viewed as a "sensitive but not specific marker of frontal lobe damage" (Alvarez & Emory, 2006, p. 19). Lower scores indicate better "cool" executive function.

　　　　Benton's Judgment of Line Orientation-Form H (BJLO; Benton, Varney, & Hamsher, 1978*).* This is a standardized measure of "pure" visuospatial processing used to provide discriminant validity for EF. The spiral-bound booklet contains 35 stimuli (i.e., 5 practice items, 30 test items) with 11 response choices (i.e., lines). Validity and reliability of this task are high (.84; Riccio & Hynd, 1992). Higher scores indicate better visuo-spatial skills.

Autonomic Functioning: Heart Rate Variability (HRV)

　　　　HRV is a measure of parasympathetic control over the heart that is an index of self-regulatory capacity (Segerstrom & Solberg Nes, 2007). Parasympathetic activity leads to more variable intervals between heart beats, and therefore higher HRV. The Ambulatory Monitoring System (Vrije Universiteit, Amsterdam, The Netherlands) was used during a 5-minute baseline period (prior to the administration of any other measures) to produce an electrocardiogram (and provide indexes of HR and HRV), with leads attached to the forearms and leg in a Lead II configuration. The electrocardiogram was sampled at 1,000 samples/s. Beats per min and mean squared successive differences in the inter-beat interval (HRV) were calculated on-line and stored in 30-second epochs. HRV was calculated as the root mean squared successive differences in the inter-beat interval (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and

22

was examined in relation to self-regulatory abilities across domains as assessed by self-report measures and neuropsychological testing.

Metabolic Functioning: Glycosylated Hemoglobin

Hemoglobin A1c (A1c) was measured to assess the overall effectiveness of blood glucose control over the past 2-3 months. Given that the long-term self-regulatory capacity and its practical impact on functioning were of interest in the current study, A1c was an appropriate glucose test as it reflects the course of glucose control over a more extended time period than other glucose measures and therefore, it is less sensitive to short-term fluctuations. The optimal level of A1c is debated, but it is generally suggested the estimate not exceed 6% for normal individuals and 7% for diabetic individuals (American Diabetes Association, 2007). Thus, lower values generally reflect "better" functioning. This measure was taken on site using the A1c NOW+ monitor (Metrika), which involved obtaining a drop of blood via finger stick delivered by a lancet device.

Well-being Measures

McGill Quality of Life Questionnaire (MQOL). This is a 16-item self-report scale measuring subjective well being in terminally ill populations (Cohen, Mount, Strobel, & Bui, 1995). Four of the five sub-scales relating to physical well being, psychological well being, existential well being, and social support comprise a total score (α=.80), which was used in the current study (i.e., the 3-item physical symptoms subscale will be excluded). Items are measured on a Likert-scale ranging from 0 to 10, with lower scores indicating poor quality of life and higher scores indicating good quality of life. The internal consistency of patients on this scale was .90.

Quality of Life in Life Threatening Illness Family Carer Version (QOLLTI-F; Cohen, Leis, Kuhl, Charbonneau, Ritvo, & Ashbury, 2006). This is a 16-item measure of caregiver

well being that takes the perception of the condition of the patient into account. This scale, derived based on what caregivers state is most important to their well being, is composed of 7 domains (i.e., carer's own state, environment, carer's outlook, quality of care, relationships, patient condition, financial) that have acceptable internal consistency ($\propto$=.48 (environment)-.81 (carer's own state)) as well as test-retest reliability (.50-.79). The internal consistency of the total score (i.e., the average of the 7 domain scores) in this caregiver sample was .90. Higher scores indicate better QOL.

Revised Dyadic Adjustment Scale-satisfaction item (RDAS; Busby et al., 1995). Patients and caregivers rated their current satisfaction in their relationship on a 0-100 scale (0= completely unhappy, 100=completely happy).

Potential Confounds

Functional Status. The ALS Functional Rating Scale (ALS-FRS) is a 12-item self-report scale used to assess activities of daily living for people with ALS (e.g., speech, handwriting, dressing/hygiene, walking; ACTS, 1996). The scale consists of 4 scales relating to coordinated upper limb motions, bulbar function, breathing, and gross, less finely controlled activities. The total score averages item responses (α=.90). Item test-retest reliability has been demonstrated ($\geq$.88). Consensus ratings between patients and caregivers assess the difficulty of specific tasks. Lower scores on a 1 to 4 scale indicate more functional difficulty. The internal consistency of this scale in the current study was .83.

Intelligence. Standard Progressive Matrices (SPM; Raven, 1948) is a multiple-choice, non-verbal abstract reasoning test that is one component of Spearman's g (general intelligence; Strauss, Sherman, & Spreen, 2006). This 60-item test involves patients selecting one missing piece from 6 or 8 alternative missing pieces to complete a stimulus figure. The test has high internal consistency (> .70; Burke, 1985) and test-retest reliability (>.80; Raven, 2000).

Data Analysis

Alpha was set at .05, two-tailed, for all inferential tests. Continuous predictors were centered prior to regression analyses.

Missing data were imputed from the available data using SPSS Missing Value Analysis. This procedure imputes missing values through expectation maximization (EM) algorithms. Reasons for missing data included: patient fatigue, time constraints, inability to reschedule, and caregiver non-response. The following is the breakdown of missing variables that required imputation. For patients, data were imputed for the BRIEF-A, JLO, RS, CNSLS, FNE, and MQOL for 1 individual each. For caregivers, 2 participants failed to complete the BRIEF-A Informant Report and 1 participant failed to complete all questionnaires including demographics and SR measures. However, these data are believed to be missing at random (MAR), which is a typical and relatively safe assumption, and thus accommodated by our analyses (Schafer & Graham, 2002).

Prior to primary analyses, preliminary analyses were conducted. First, despite having small sample sizes, t-tests and chi-square tests examined demographic differences between patients with ALS (N=31) and PLS (N=6). ALS and PLS patients significantly differed with regard to gender (X^2 (1, 37) = 4.03, $p < .05$) and marital status (X^2 (1) = 12.15, $p < .01$), such that ALS patients were more likely to be male and married than PLS patients. However, t-tests revealed a lack of significant differences between these groups on nearly all substantive variables. Only 1 of the 18 comparisons was significant at $p < .05$. When comparing A1c values of patients without diabetes to those with type 2 diabetes (N=3), there were no significant differences, suggesting that diabetes status should not be statistically controlled in analyses.

The test of **Hypothesis 1** primarily involved exploratory data analyses to examine the distributions of each dependent variable. First, univariate analyses (i.e., descriptive statistics and scatterplot/boxplot examination) revealed outliers in the data, the degree and direction of asymmetry of the distribution (skewness), and the peakedness of the distribution (kurtosis) of each variable. Given that skewness statistics can be misleading, especially in small samples, a conservative approach was taken in evaluating when to remove outliers or transform data. In this study, variables with skewness statistics that were ≥ 2 standard errors were examined for removal of outlier(s) and considered for transformation. However, given that there is no universally applicable rule of thumb in interpreting these estimates, histograms and residual plots were closely examined before data transformation. When appropriate, data were log transformed to achieve a normal distribution. This examination of the distribution of values not only identifies whether deficits exist on a continuum or not, but it also informs whether there are subsequent constraints on r and whether the assumptions of regression analyses are violated with regard to linearity and normality of the dependent variables.

The test of **Hypothesis 2**, regarding patient-caregiver agreement, involved 4 primary components. First, paired samples T-tests were conducted to examine mean-level differences between patients and caregivers. Next, a correlation matrix was calculated to determine if there is a positive (e.g., moderate) correlation between raters. Next, scatterplots were examined to detect curvilinearity. Finally, non-linear relationships were then entered into a curve estimation regression (simultaneously) to examine the nature of the relationship.

Post-hoc analyses were conducted to examine discrepant patient-caregiver ratings of SR. First, this involved the creation of a discrepancy score (patient rating-caregiver rating) for each scale on which there was disagreement between patient and caregiver reports. Next, these discrepancy scores were regressed onto the neuropsychological measures of EF to

26

determine whether differences in executive functioning contributed to patient-caregiver discrepancies. The first step included the main effects (i.e., "cool" EF, "hot" EF) and the second step included the main effects and their interaction ("cool" EF* "hot" EF). The interactions were probed to examine the nature of the differences between the main effects for patients and caregivers. Last, repeated-measures regressions examined within-subject effects of person (i.e., patient v. caregiver) on the interaction between "cool" EF and "hot" EF performance in predicting SR. The "person" factor had 2 levels (i.e., patient report and caregiver report) and the 3 covariates were performance on the WCST, IGT, and the interaction (i.e., WCST*IGT).

A similar procedure was used to test **Hypothesis 3**, which involved computation of a correlation matrix to examine the relationships among the various measures of SR and EF. The use of composite indices of EF (e.g., "cool" EF, "hot" EF) and SR (e.g., emotional lability, rumination, social anxiety, dyadic cohesion, and global regulation) would be justified by moderate to high correlations ($r \geq .30$) with related constructs and weaker relationships ($r \leq .10$) with divergent measures. A lack of support for composite constructs would result in each scale being examined separately in subsequent analyses.

Zero-order correlations were examined to test **Hypothesis 4**, that superior "hot" and "cold" EF would be associated with better self-regulatory ability across domains. The need to statistically control for some variables (e.g., intelligence, time of assessment, respiratory functioning, and functional status) was examined. In general, examination of partial correlations revealed that the relationship between caregiver ratings of rumination and patients' "cool" EF may be attributed to the overlap between IQ and EF.

The test of **Hypothesis 5** was similarly conducted by examining zero-order correlations among facets of SR and measures of physiological functioning. Again, the need to statistically

control for some variables (e.g., intelligence, time of assessment, respiratory functioning, and functional status) was explored, but was largely unnecessary given the lack of significant relationships.

Hypothesis 6 involved the computation of a correlation matrix to determine if better self-regulatory abilities and physiological functioning would predict better QOL and more relationship satisfaction for patients and caregivers. Again, given the lack of relationship between potential confounders (e.g., age, gender, time of assessment, ventilation status, and functional status) and the variables of interest (i.e., QOL, relationship satisfaction), no statistical controls were included in analyses and zero-order correlations were sufficient to examine these relationships. Additional hierarchical regressions were employed to examine the unique contribution of caregiver ratings to patients' ratings of QOL, above and beyond patient ratings, and vice versa. Thus, patient QOL was regressed onto patient ratings of SR in step 1 and caregiver ratings of SR in step 2. Similarly, in a second regression, caregiver QOL ratings were regressed onto caregiver ratings of patient SR in step 1 and patient ratings in step 2.

Table 2.1
Descriptive Characteristics of Sample

Variable	Patients	Caregivers
Age	59.97 (11.57)	58.33 (13.31)
Gender		
Male	54.1 % (N=20)	27 % (N=10)
Female	45.9% (N=17)	70 % (N=26)
Ethnicity		
Caucasian	97 % (N=36)	95 % (N=35)
Latino	3 % (N=1)	3 % (N=1)
Marital Status		
Married	84 % (N= 31)	
Divorced	8 % (N= 3)	
Widowed	5% (N= 2)	
Single	3% (N=1)	
Education (years)	13.81 (3.73)	
Household Income (annual)	$53,151 ($32,477)	
Disease Type:		
ALS	84 % (N=31)	
PLS	16 % (N=6)	
Onset Type:		
Limb	78 % (N=29)	
Bulbar	22 % (N=8)	
Months Since Diagnosis	36.02 (34.52)	
Months Since Onset	57.65 (42.66)	

Functional Status (ALS-FRS)	30.66 (9.19)
Response Mode:	
Verbal	81 % (N=30)
Non-Verbal	19 % (N=7)

Note. 75% of the patients' caregivers were a spouse living in the same household

Chapter Three

Results

Distribution of SR and EF in Patients

Descriptive statistics revealed that most continuous variables were normally distributed. Examination of skewness statistics, scatterplots, and boxplots revealed no problematic outliers or significant skewness for most variables (see Table 2). However, there were 2 variables for which the skewness statistic was ≥ 2 standard errors, which warranted consideration for transformation. Upon examining the distribution of the WCST variable (skewness = 1.04, SE=.39), the slight positive skew looked acceptable on a boxplot. There were no significant outliers and data were continuously distributed. Thus, this variable was not transformed. On the other hand, the HRV data (i.e., MSSD), which was also positively skewed (skewness = 2.94, SE=.39), evidenced several outliers. These outliers were closely examined and considered for removal from the data. However, only 2 data points (426.60, 592.67) were removed due to them falling outside the typical range of MSSD values (i.e., < 290) as established in a large undergraduate sample (N=166) using the same equipment and software. The other outliers (274.22, 238.08, 182.46) were not removed because they were within the range of reasonable MSSD values. The removal of these 2 outliers however, did not entirely correct the skewness of this variable. Thus, the data was also log transformed (i.e., $\log_{10}$) to achieve a normal distribution (skewness =.34, SE=.40).

Thus, normal and continuous distributions suggest that self-regulatory and executive impairments in ALS do exist on a spectrum, rather than as discrete disease entities, as predicted in Hypothesis 1.

The first part of Hypothesis 2 proposed positive correlations between patient and caregiver ratings of patient SR function. The correlations in Table 3 revealed that patient-caregiver agreement in rating SR and EF ranged from weak to strong, but was generally positive (range: -.14-.58; mean r = .10). Specifically, there was strong agreement with regard to emotional lability (r = .58; p < .01), such that as caregivers perceived more lability, patients also perceived more lability. Likewise, there was a moderate to strong positive relationship between patients' and caregivers' report of patients' social anxiety (i.e., BFNE; r = .43, p < .01). Patient and caregiver reports of patients' global regulation were also moderately correlated (r = .31, *ns*). However, there was less patient-caregiver agreement on cohesion (r = .19, ns), and there was virtually no relationship between patient and caregiver ratings of rumination, that is, patients' ability to regulate thought processes (r = .15, *ns*), indicating that patient-caregiver reports of relationship cohesion and patient ability to regulate thought processes were more discrepant. Therefore, this part of Hypothesis 2 was partially supported: Moderate to high patient-caregiver agreement characterized emotional and more global measures of patient SR, but there was little agreement on cognitive measures of SR and, surprisingly, on cohesion in the patient-caregiver relationship.

The second part of Hypothesis 2 proposed mean differences between patients and caregivers such that patients would perceive themselves to have better SR function than would caregivers. Table 3 includes means and standard deviations for the SR measures for patients and caregivers. Paired samples T-tests revealed no significant mean level differences between patient and caregiver ratings of emotional lability (t(1, 35) = 1.74, *ns*) or social anxiety (t(1, 35) = 1.26, *ns*). However, there was a significant difference between patient and caregiver reports of patients' global regulation (t(1, 35) = 2.15, p < .05), such that caregivers perceived

patients to be functioning better than patients perceived themselves to be functioning. There

was also a significant difference between patient and caregiver reports of relationship cohesion

($t(1, 35) = 2.27$; $p < .05$), where caregivers perceived more cohesion than patients. Therefore,

these results are opposite the predicted pattern in Hypothesis 2, which suggested that patients

would perceive themselves to be functioning better than caregivers perceived them to be

functioning.

  The final part of Hypothesis 2 proposed that disagreements between patient and

caregiver reports could arise from nonlinear relationships or patients' cognitive function.

These possibilities were explored with regard to cohesion and rumination, where there was

disagreement. Curve estimation regression revealed a non-linear, quadratic relationship

between patient and caregiver reports of dyadic cohesion ($\beta=.42$, $F(2,36)= 4.27$, $p < .05$, $\Delta R^2=$

.16). Although there was a tendency for patients to rate cohesion as low compared to

caregivers, the highest agreement occurred at lower scores (i.e., when cohesion was higher)

and to a lesser degree, at agreement at higher scores (i.e., when cohesion was lower). While

caregivers perceived high cohesion and patients perceived low cohesion in some instances, the

opposite pattern in which patients perceived high cohesion and caregivers perceived low

cohesion, did not emerge (see Figure 1). Post-hoc analyses of patient-caregiver discrepancies

on rumination and cohesion attempted to examine the contribution of EF to these

discrepancies. Thus, the discrepancy score for each scale was regressed onto EF measures

(WCST, IGT) in separate analyses. A lack of significant effects (rumination discrepancy

$\rightarrow$"cool" EF: $t(1,35)= 1.19$, *ns*; rumination discrepancy $\rightarrow$"hot" EF: $t(1,35)= .02$, *ns*; cohesion

discrepancy $\rightarrow$"cool" EF: $t(1,35)= 1.82$, *ns*; cohesion discrepancy $\rightarrow$"hot" EF: $t(1,35)= -.17$,

ns) indicated that these discrepant views of patient's self-regulatory capacity could not be

explained by differences in executive capacity.

However, it was suspected that the interaction of the EF measures (WCST*IGT) may account for more variance in SR than each measure alone. Also, to explore whether the effects of the interaction on SR differed depending on the rater (e.g., patient v. caregiver), repeated measures regressions examined the within-subject effect of person on the interaction between "hot" and "cool" EF. There was a tendency ($p < .10$) for the interaction to predict dyadic cohesion differently for patients and caregivers. For patients, good "hot" EF was associated with more cohesion only if there was also good "cool" EF. Good "hot" EF was associated with less cohesion if there was poor "cool" EF for patients. Poor "hot" EF was generally related to less cohesion for patients, and this was most true if patients had good "cool" EF (see Figure 2). The opposite pattern emerged for caregivers, such that poor "hot" EF was generally associated with more cohesion, and this was most true if patients had good "cool" EF. On the other hand, good "hot" EF was associated with more cohesion if there was poor "cool" EF (see Figure 3). Finally, when patients had good "cool" EF, caregivers rated patients as less likely to ruminate, and this was especially true when patients also had good "hot" EF.

Thus, results partially align with Hypothesis 2, in that there was a non-linear relationship between patient and caregiver ratings of dyadic cohesion. However, patients and caregivers agreed most when both perceived more cohesion. This pattern was not explained by "hot" or "cool" EF.

Are Self-Regulation Measures Unitary?

The first part of hypothesis 3 aimed to establish construct validity for SR. A correlation matrix revealed that the relationships among various domains of SR varied for both patients (see Table 4) and caregivers (see Table 5). Patients' reports of SR capacities in different domains were generally in the weak to moderate range (range: -.17-.60; mean $r =$ .20), and were less consistent than caregivers' (range: -.13-.51; mean $r = .30$). There was a

strong, positive correlation between patients' reported social anxiety and rumination, such that as patients perceived less social anxiety, they perceived less rumination ($r = .60, p < .01$). Patients' global regulation correlated most strongly and consistently with other measures of self-regulation. Thus, as patients perceived themselves as having more global regulatory ability, they perceived themselves as being less emotional labile, less ruminative, and less socially anxious. On the other hand, better global regulation was related to perceptions of less dyadic cohesion.

In general, a similar pattern emerged for caregivers (see Table 5). However, the relationships among caregiver reports of patients' SR across domains were generally stronger. Specifically, caregivers perceptions of emotional lability, social anxiety, and dyadic cohesion converged, such that better functioning in one domain was associated with better functioning in the other domains. Similarly caregiver ratings of patient tendency to ruminate was related social anxiety in the expected direction, with more rumination associated with more social anxiety. As was true for patients, caregiver rated global regulation was most strongly and consistently correlated with other measures of SR. As caregivers rated better global regulation, they also rated less emotional lability, less rumination, less social anxiety, and to a lesser degree, more dyadic cohesion ($r = .15$, *ns*). This divergence among domains of self-regulation, which was particularly evident for patients, does not support Hypothesis 3 or the use of composite indices of SR that combine measures of SR into a single index. In general, caregivers perceived a more pervasive pattern of deficits (evidenced by higher correlations across measures) compared with patients, who viewed their deficits to be less cohesive and more idiosyncratic.

Are Cognitive Measures Unitary?

The second part of Hypothesis 3 aimed to examine the construct validity of EF. A correlation matrix (Table 6) revealed that although there was a small to moderate relationship between measures of "hot" and "cold" EF as expected, there was sufficient evidence to conceptualize these as distinct EF components. While there was a divergent relationship among measures of EF and visuo-spatial skills, intelligence was consistently associated with the other cognitive measures. Therefore, the subsequent correlations among "hot" EF, "cold" EF, and SR measures statistically controlled for intelligence. Hypothesis 3 was supported in that "hot" and "cool" EF were more strongly correlated to one another than to an unrelated construct.

How much does EF contribute to SR?

Hypothesis 4 proposed that EF would contribute to SR. Given the lack of support for composite SR and EF constructs, "hot" and "cool" components of EF were examined in relation to individual domains of SR (i.e., thought regulation, social anxiety, emotion regulation, global regulation), primarily using zero-order correlations. However, given the significant relationship among intelligence and both EF and SR constructs, a separate set of correlations controlled for intelligence (see Table 7). Specifically, higher intelligence was related to better "hot EF" ($r = -.34, p < .05$), more social anxiety (patient rated; $r = .35, p < .05$), less dyadic cohesion (caregiver rated; $r = .47, p < .01$), and less rumination (caregiver rated; $r = -.41, p < .01$). There was no need to statistically control for other suspected confounds (e., respiratory functioning, time of assessment, and functional status).

Correlations between EF performance and SR reports were generally in the small to medium range. Better "cool" EF significantly correlated with less rumination by caregiver report (but not by patient report). This relationship was no longer significant when

intelligence was partialled out. Smaller, non-significant correlations suggested that better "cool" EF also related to better relationship cohesion by patient report, but worse cohesion by caregiver report. There were no significant correlations between "hot" EF and SR. Again, smaller, non-significant correlations suggested that better "hot" EF was related to better relationship cohesion by patient report and worse cohesion by caregiver report. This pattern of results is largely reflected in Figures 2 and 3, which show the effects of EF on patient and caregiver reports of cohesion.

In sum, the contribution of EF to SR depended on several factors, including the EF component (i.e., "hot" v. "cool"), the individual rating patient self-regulatory capacity, and the domain of SR. Consequently, Hypothesis 4 is partially supported.

Physiological Functioning: Does EF or SR matter?

Hypothesis 5 proposed that better "cool" and "hot" EF, and better ability to self regulate across domains, would be associated with more optimal metabolic (i.e., lower A1c) and autonomic functioning (i.e., higher HRV). First, though not an explicit hypothesis, better physiological health was expected to converge across measures of metabolic and autonomic functioning. However, this relationship between A1c and HRV did not hold ($r = -.05$; *ns*). Thus, support for the hypothesized relationships between EF and SR were limited by the divergence of these two physiological measures.

As shown in Table 8, correlations among autonomic functioning (i.e., HRV) and measures of SR and EF were generally in the small to medium range. For patients, less emotional lability was significantly related to higher (i.e., more optimal) HRV.[2] On the other hand, better "cool" EF was significantly related to lower HRV. Smaller, non-significant

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[2] A significant relationship between HRV and patient age ($r = .45$, $p < .01$), did not significantly change the relationship between emotional lability and HRV or the relationship between WCST performance and HRV when it was statistically controlled in step 1 of a hierarchical regression. Thus, to preserve power (i.e., more df), zero-order correlations were preferred.

correlations suggested that less rumination, less social anxiety, and more global regulation were related to higher HRV and better autonomic functioning. While there were no significant relationships between caregiver rated SR and patients' HRV, correlations revealed a relationship between less emotional lability, more relationship cohesion, less social anxiety, better global regulation, and higher HRV. In sum, as expected in Hypothesis 5, better autonomic functioning was related to better SR in several domains (albeit these relationships were not always statistically significant). However, "hot" and "cool" EF did not relate to HRV in the expected direction, as better EF was associated with lower (i.e., worse) HRV.

Correlations among measures of SR, EF, and metabolic functioning were generally smaller in magnitude than those with autonomic functioning, and this was most true for patients. Although largely non-significant, correlations were generally small to moderate in size. There was convergence between patient and caregiver ratings of global self-regulation, such that better perceptions of global self-regulation were significantly associated with better regulated glucose (i.e., lower A1c)[3]. Smaller, non-significant correlations indicated that the pattern of relationships was stable for both patients and caregivers, such that for both raters, less emotional lability, less rumination, less social anxiety, better global regulation, and more dyadic cohesion were associated with lower (i.e., better) A1c values. Again, Hypothesis 5 was partially supported with regard to the relationships between metabolic functioning and global self-regulation. However, on the whole, results did not converge across measures of physiological functioning suggesting that different components of SR and EF may be more or less important for optimal physical functioning, depending on the physiological parameter examined.

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[3] A significant relationship between A1c and time of assessment ($r = .38$, $p< .05$), did not significantly change the relationship between global regulation and A1c for patients or caregivers. Thus, to preserve power (i.e., more df), zero-order correlations were preferred.

Patient and Caregiver QOL: What really matters?

Hypothesis 6 proposed that better functioning across domains of SR, "hot" and "cold" EF, and better physiological functioning would contribute to better QOL for both patients and caregivers. A correlation matrix including patient and caregiver ratings of SR, EF, and QOL informed the contribution of SR (as rated by both patients and caregivers) to QOL (as rated by both patients and caregivers). Results are shown in Table 9. Although not an explicit hypothesis, the relationship between patient and caregiver QOL and relationship satisfaction were of interest. Correlations revealed that these relationships were weak (QOL: $r = .12$, *ns*; relationship satisfaction: $r = .21$, *ns*), which is consistent with previous research.

First, patient perceptions of SR were moderately associated with patients' QOL. When patients perceived less rumination, more dyadic cohesion, and less social anxiety, they rated significantly better QOL. Smaller, non-significant correlations revealed a similar pattern for emotional lability and global regulation, such that better functioning was related to better QOL. While better "cool" EF appeared to positively relate to QOL, better "hot" EF was related to worse QOL for patients. With regard to physiological functioning, lower levels of A1c (i.e., better metabolic functioning) and higher HRV (i.e., better autonomic functioning) were related to better QOL as rated by patients, although these correlations did not reach significance. In sum, Hypothesis 6 was generally supported with regard to patient QOL, as better SR, better "cool" EF, and better physiological functioning were associated with better QOL.

Not surprisingly, patient perceptions of SR were not as strongly or consistently related to caregivers' ratings of QOL. Correlations between patients' ratings of SR and EF and caregiver rated QOL were generally weak and non-significant. This idiosyncratic pattern of

results indicates that patient reports of SR, as well as their EF and physiological functioning, are less important to caregiver QOL, which does not support Hypothesis 6.

Given that patient ratings of SR were more closely related to patient rated QOL, a similar pattern was expected to emerge for caregiver ratings of patients' SR and caregiver rated QOL, given shared rater variance. Although caregivers' QOL was not significantly influenced by their perceptions of patients' self-regulatory functioning in any domain, as reflected by weak to moderate, non-significant correlations, caregiver ratings of SR were generally correlated with their QOL more strongly than patient ratings of SR, when comparing domains (except dyadic cohesion). Caregiver perceptions of patient SR were less important to patient rated QOL, as reflected in generally weak, non-significant correlations. In sum, ratings of SR, EF, and physiological functions appeared to be most convergent when the rater was the same (i.e., when patients' SR ratings were correlated with patient QOL, when caregiver SR ratings were correlated with caregiver QOL).

Given the lack of strong and significant correlations between ratings of SR and QOL, even when rated by the same individual, a series of hierarchical regressions was conducted to examine other factors that might contribute to QOL ratings, above and beyond an individual's perception of SR. Although patient perceptions clearly influenced their own QOL more than their caregiver's QOL, and vice versa, the contribution of the "other rater" to self-ratings remained unclear. That is, the incremental contribution of others' perceptions, above and beyond self perceptions, to QOL were examined for both patients and caregivers. Caregivers' ratings' of patients' SR abilities accounted for 2% of the variance in patients' QOL, above and beyond patients' own perceptions. On the other hand, when predicting caregiver QOL, patients' perceptions of their self-regulatory abilities accounted for an additional 7% of the variance in caregiver QOL, above and beyond caregivers' own perceptions of patients'

functioning. In sum, patients' perceptions of their SR abilities appeared to contribute more to

caregiver QOL than caregivers' perceptions contributed to patients' QOL.

The last component of Hypothesis 6 involved relationship satisfaction, as rated by both

patients and caregivers. Specifically, better SR, EF, and physiological functioning were

expected to correlate with more satisfaction, as rated by both patients and caregivers. A

correlation matrix (see Table 4) revealed a similar pattern of generally weak to moderate

relationships, especially for patient ratings of SR, EF and physiological functions. Patient

ratings of SR significantly contributed to patient relationship satisfaction in a single domain,

dyadic cohesion ($r = -.38$, $p < .05$). The relationships among other patient ratings were

generally in the expected direction, but were weak to moderate, and non-significant.   Patient

ratings similarly contributed little to caregiver ratings of relationship satisfaction. The pattern

of relationships among patients' SR, EF, and physiological functions was again, more

idiosyncratic. While there was a significant correlation between patients' "hot" EF and

caregiver relationship satisfaction, it was opposite the expected direction, with better "hot" EF

corresponding to worse relationship satisfaction for caregivers. While patient ratings of SR

were generally weakly and inconsistently related to relationship, caregiver ratings reflected a

different pattern.

In general, caregiver ratings of patient SR were moderately and consistently related to

relationship satisfaction, for both patients and caregivers. That is, when caregivers perceived

patients to have more SR, both patients and caregivers rated higher relationship satisfaction.

Although only one correlation reached significance (dyadic cohesion/caregiver relationship

satisfaction, $r = -.59$, $p < .01$), caregivers' ratings of patient SR across domains converged,

supporting the idea that caregivers hold a more global view of deficits compared to patients.

This global view, whether pertaining to self-regulatory strength or deficit, appears to

contribute to relationship quality for both patients and caregivers. In general, these results partially supported Hypothesis 6, that better SR would correspond to better relationship satisfaction. This was most true when caregivers rated patients SR.

Table 3.1

Distribution Statistics of Variables of Interest

	Skewness Statistic (SE=.388)	
Measure	Patient	Caregiver
WCST	1.038	-
IGT	-.364	-
JLO	-.322	-
SPM	-.534	-
A1c	-.707	-
MSSD	2.943[a], .335[b]	-
BRIEF A	.388	.701
CNSLS	.927	.212
RS	-.645	-.173
BFNE	.528	.509
RDAS	.638	.377
ALS-FRS	-.128	-
QOL	-.857	-.329

Note. WCST = Wisconsin Card Sorting Test; IGT = Iowa Gambling Test; JLO = Judgment of Line Orientation Test; SPM= Standard Progressive Matrices; A1c = glycosolated hemoglobin; MSSD = heart rate variability; BRIEF-A = Behavior Rating of Executive Functions-Adult version; CNSLS = Center for Neurologic Study- Lability Scale; RS = Rumination Scale; BFNE = Brief Fear of Negative Evaluation Scale; RDAS = Revised Dyadic Adjustment Scale; ALS-FRS= Amyotrophic Lateral Sclerosis Functional Rating Scale; QOL= Quality of Life

[a]Skewness statistic prior to transformation; [b]Skewness statistic following transformation.

Table 3.2

Inter-correlations Among Patient and Caregiver Reports of Patients' Self-Regulatory Capacity

Caregiver Ratings		Patient Ratings				
Variable	M (SD)	Emotional Lability	Rumination	Lack of Cohesion	Social Anxiety	Global Dysregulation
		4.21 (5.45)	-15.09 (4.36)	8.02 (4.23)	28.63 (11.81)	95.89 (17.94)
Emotional Lability	12.89 (4.47)	.581**	-.031	-.032	.152	.196
Rumination	-15.33 (4.10)	-.136	.148	.001	-.139	.299
Lack of Cohesion	6.19 (3.41)	.232	-.068	.192	.159	.045
Social Anxiety	25.97 (12.12)	.090	.152	-.068	.425**	.050
Global Dysregulation	88.30 (18.62)	.035	.074	-.257	.125	.312

Note. Emotional Lability, Center for Neurologic Study- Lability Scale; Rumination, Rumination Scale; Lack of Cohesion, Revised Dyadic Adjustment Scale; Social anxiety, Fear of Negative Evaluation Scale; Global Dysregulation, Behavior Rating of Executive Functions-Adult version.

p < .05; **p* < .01.

Table 3.3

Inter-correlations Among Patients' Ratings of Self-Regulation Across Domains

Variable	Emotional Lability	Rumination	Lack of Cohesion	Social Anxiety	Global Dysregulation
Emotional Lability	1	.100	.125	.167	.325*
Rumination		1	-.047	.597**	.456**
Lack of Cohesion			1	.064	-.170
Social Anxiety				1	.224
Global Dysregulation					1

Note. Emotional Lability, Center for Neurologic Study- Lability Scale; Rumination, Rumination Scale; Lack of Cohesion, Revised Dyadic Adjustment Scale; Social anxiety, Fear of Negative Evaluation; Global Dysregulation, Behavior Rating of Executive Functions-Adult version.

p < .05; **p* < .01.

Table 3.4

Inter-correlations Among Caregivers' Ratings of Self-Regulation Across Domains

Variable	Emotional Lability	Rumination	Lack of Cohesion	Social Anxiety	Global Dysregulation
Emotional Lability	1	.180	.395*	.353*	.440**
Rumination		1	-.130	.347*	.513**
Lack of Cohesion			1	.196	.146
Social Anxiety				1	.347*
Global Dysregulation					1

Note. Emotional Lability, Center for Neurologic Study- Lability Scale; Rumination, Rumination Scale; Lack of Cohesion, Revised Dyadic Adjustment Scale; Social anxiety, Fear of Negative Evaluation; Global Dysregulation, Behavior Rating of Executive Functions-Adult version.

p < .05; **p* < .01.

Table 3.5

Inter-correlations Among Measures of Neuropsychological Functioning

Measure	Poor "cool" EF	Poor "hot" EF	Visuo-spatial skills	Intelligence
Poor "cool" EF	1	.246	-.196	-.416*
Poor "hot" EF		1	-.147	-.338*
Visuo-spatial skills			1	.573**
Intelligence				1

Note. Poor "cool" EF = Wisconsin Card Sorting Test; Poor "hot" EF = Iowa Gambling Test; Visuo-spatial skills = Judgment of Line Orientation Test; Intelligence = Standard Progressive Matrices.

p < .05; **p* < .01.

Table 3.6

Inter-correlations Among Measures of Executive Functions and Self-Regulation

SR Domain		EF Measures			EF Measures (IQ Partialled)	
		Poor	Poor		Poor	Poor
	M (SD)	"cool" EF	"hot" EF	Intelligence	"cool" EF	"hot" EF
Patients' Ratings		18.68 (13.33)	10.59 (31.46)	38.51 (12.75)		
Emotional Lability	14.21 (5.45)	-.162	-.090	.116	-.126	-.054
Rumination	-15.09 (4.36)	.082	.047	-.078	.055	.0
Lack of Cohesion	8.02 (4.23)	.214	.151	-.064	.207	.137
Social Anxiety	28.63 (11.81)	.089	.016	.346*	.273	.151
Global Dysregulation	95.89 (17.95)	-.057	-.090	-.081	-.100	-.125
Caregivers' Ratings						
Emotional Lability	12.89 (4.47)	-.070	-.066	.188	.009	-.003
Rumination	-15.33 (4.10)	.354*	.045	-.407*	.222	-.108
Lack of Cohesion	6.19 (3.41)	-.155	-.212	.467**	.049	-.065
Social Anxiety	25.67 (12.12)	.137	.039	-.003	.150	.041

| Global Dysregulation 88.30 (18.62) | .095 | .006 | -.160 | | .032 | -.052 |

Note. Emotional Lability, Center for Neurologic Study- Lability Scale; Rumination, Rumination Scale; Lack of Cohesion, Revised

Dyadic Adjustment Scale; Social anxiety, Fear of Negative Evaluation Scale; Global Dysregulation, Behavior Rating of Executive

Functions-Adult version; Poor "cool" EF = Wisconsin Card Sorting Test; Poor "hot" EF = Iowa Gambling Test; Intelligence =

Standard Progressive Matrices.

p < .05; **p* < .01.

Table 3.7

Inter-correlations Among Patients' Physiological Functions and Self-Regulation

	Patients' Functioning	
Self-Regulation Measure	HRV	A1C
Patient Ratings		
M (SD)	1.51 (.42)	5.38 (.45)
Emotional Lability	-.344*	.054
Rumination	-.193	.258
Lack of Cohesion	.072	.000
Social Anxiety	-.195	.134
Global Dysregulation	-.190	.427**
Poor "cool" EF	.342*	.010
Poor "hot" EF	.199	.105
Caregiver Ratings		
Emotional Lability	-.258	.150
Rumination	.261	.243
Lack of Cohesion	-.174	.205
Social Anxiety	-.140	.285
Global Dysregulation	-.077	.328*

Note. Caregivers did not complete the WCST and IGT tasks; Emotional Lability, Center for Neurologic Study- Lability Scale; Rumination, Rumination Scale; Lack of Cohesion, Revised Dyadic Adjustment Scale; Social anxiety, Fear of Negative Evaluation Scale; Global Dysregulation, Behavior Rating of Executive Functions-Adult version; Poor

"cool" EF = Wisconsin Card Sorting Test; Poor "hot" EF = Iowa Gambling Test;

Intelligence = Standard Progressive Matrices.

*p<.05; **p<.01

Table 3.8

Inter-correlations Among Self-Regulation, Quality of Life, and Relationship Satisfaction

Measure	QOL		Relationship Satisfaction	
	Patient	Caregiver	Patient	Caregiver
M (SD)	66.03 (15.99)	7.49 (1.46)	86.39 (16.02)	90.36 (12.40)
Patients' Ratings				
Emotional Lability	-.161	.110	-.224	.094
Rumination	-.349*	.005	-.023	-.013
Lack of Cohesion	-.403*	-.284	-.377*	-.083
Social Anxiety	-.500**	-.111	-.204	-.046
Global Dysregulation	-.200	-.057	.069	-.213
Poor "cool" EF	-.193	.117	-.205	.068
Poor "hot" EF	.276	.251	-.216	.346*
HRV	.078	.042	.022	.195
A1c	-.154	.314	-.086	-.103
Caregivers' Ratings				

Emotional Lability	-.159	-.221	-.225	-.181
Rumination	.018	-.281	-.205	-.029
Lack of Cohesion	-.214	.110	-.265	-.593**
Social Anxiety	-.140	-.114	-.306	-.289
Global Dysregulation	.151	-.131	-.250	-.174

*p<.05; **p<.01

Figure3.1

Quadratic Relationship Between Patient and Caregiver Cohesion Ratings.
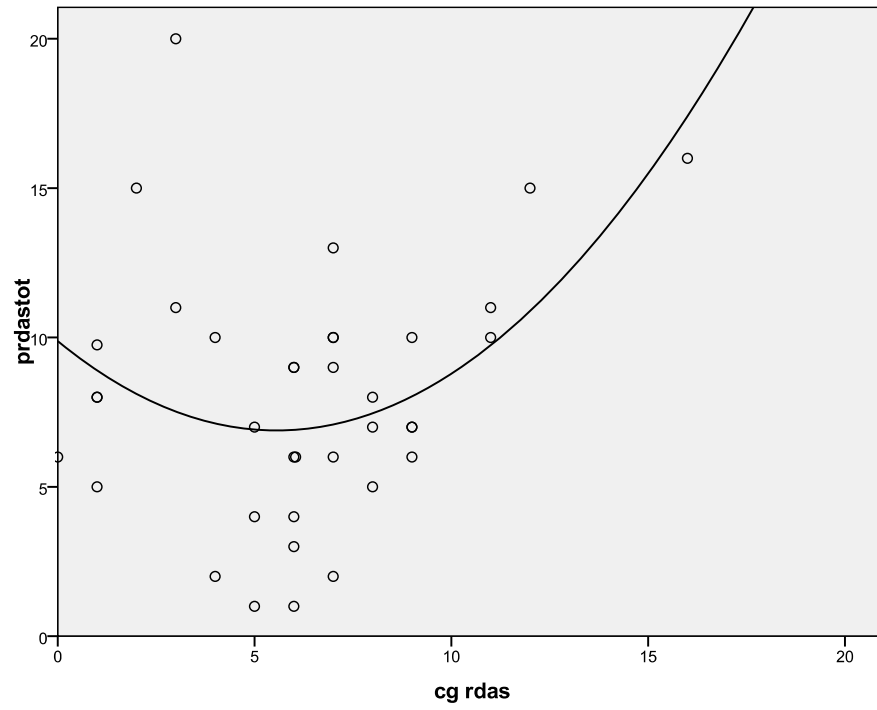
Figure 3.2

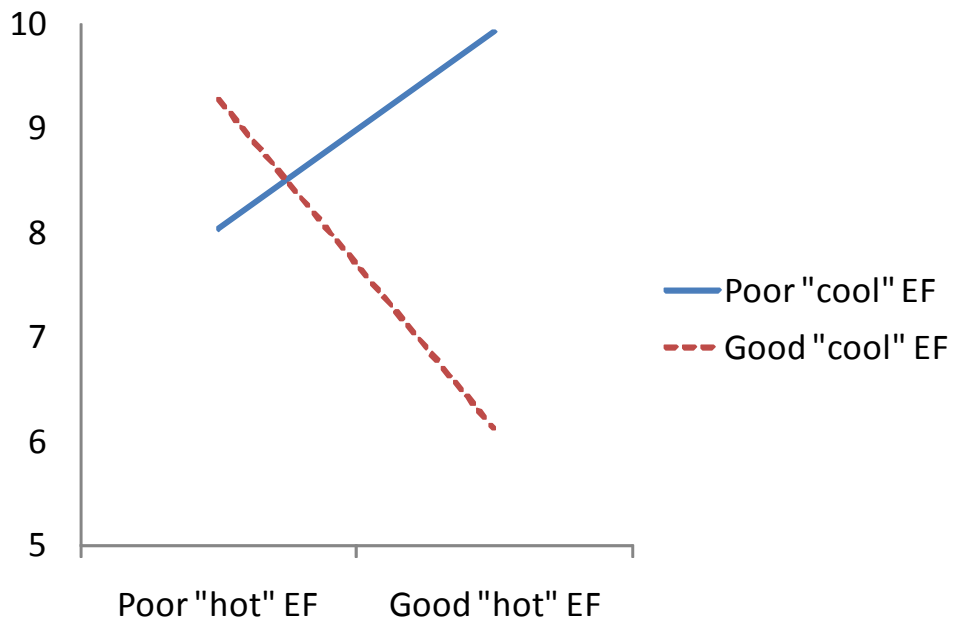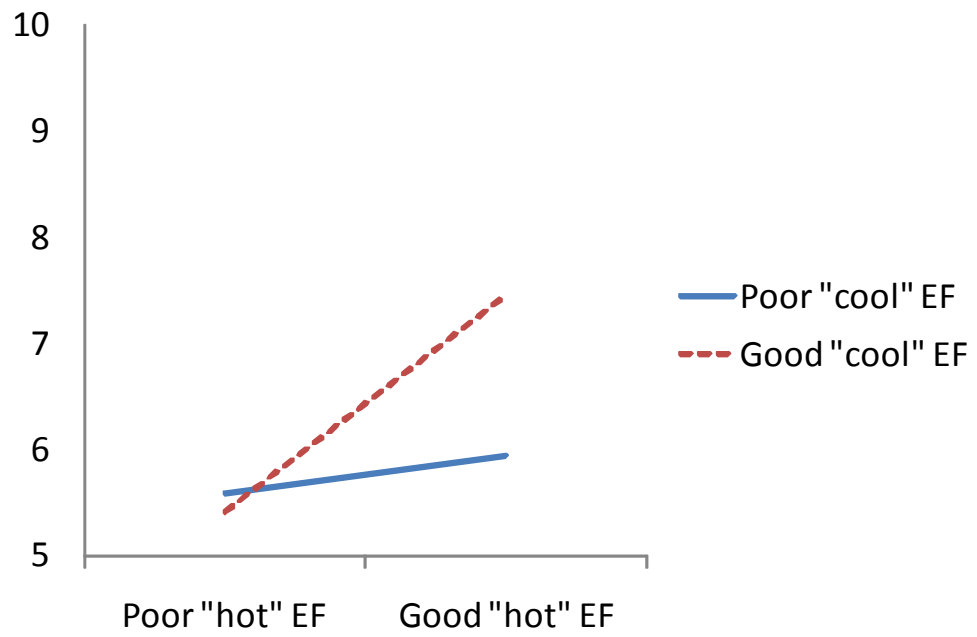Interaction of "Hot" and "Cool" EF in Predicting Patient Cohesion.

Figure 3.3

 Interaction of "Hot" and "Cool" EF in Predicting Caregiver Cohesion.

Chapter Four

Discussion

ALS is increasingly viewed as a multi-system disorder accompanied by cognitive and behavioral changes (Strong, 2001, 2008; Strong & Rosenfeld, 2003). However, an extensive body of research has failed to clarify the nature or prevalence of these extra-motor symptoms in ALS. The current study aimed to elucidate the prevalence and pattern of executive deficits and behavioral dysregulation in patients with ALS.

Does the Pattern of Self-Regulatory Deficits in ALS Reflect a "Distinct" Disorder?

This research revealed that the scope of extra-motor impairment in ALS can be wide, with deficits existing on a continuum such that some, but not all, patients evidence deficits in self-regulatory abilities to effectively manage social relationships, emotions, and thought processes. This informs research and clinical work with MND as self-regulatory deficits may be part of the disease process for some patients.

Of particular interest in this study was convergence of self-regulatory deficits across domains. Given research that executive control and behavioral self-regulation rely on a similar resource, and that expenditure of this resource on one task can impair subsequent performance on others, it was surprising that there was not a consistent pattern that emerged among domains of self-regulation, "hot" and "cold" EF, and physiological regulation. Specifically, deficits in EF were expected to correspond to behavioral deficits across domains of self-regulation as well as worse physiological functioning. Given that the IGT task, used as a measure of "hot" EF, is a more context-dependent measure representative of "real-world" situations, one might have expected to see stronger relationships among other measures of "applied" behavioral self-regulation (i.e., social anxiety, rumination, emotional lability, and global regulation). Conversely, "cool" EF was more highly correlated with various forms of

60

behavior regulation in this sample. Specifically, more emotional lability (patient-rated) was related to better "cool" EF (albeit not significantly), which is inconsistent with previous research that emotional lability relates to worse "cool" EF (McCullagh et al., 1999). On the other hand, "hot" EF was more highly correlated with patient and caregiver ratings of QOL and relationship satisfaction. It is possible that "cool" EF most strongly relates to measures assessing how people behave or act (emotional lability, dyadic cohesion) and "hot" EF relates more closely to measure of how people feel (social anxiety, quality of life). Given the related, yet distinct nature of the "hot" and "cool" components of EF, conceptualizing EF as a non-unitary construct is informative and important, especially for future studies. This may be particularly true in ALS as deficits may influence important clinically important outcomes.

Who is Most Accurate in Rating Patient Behavior?

Even more, the pattern of inter-correlations among domains of SR differed depending on who was rating patients' self-regulatory abilities. Despite a lack of significant mean-level differences between patients and caregivers, a clear tendency emerged for caregivers to rate patients' deficits more globally, such that caregiver ratings of patients' self-regulatory abilities aligned across domains (i.e., higher inter-correlations). Thus, caregiver ratings were indicative of a more pervasive pattern of decline in self-regulatory capacity compared to patients. Perhaps, it is caregivers who bear the burden of patients' inability to regulate, therefore resulting in more general or "accurate" ratings. Likewise, the impact of these deficits may be more global for caregivers than patients. On the other hand, it is possible that caregivers are most psychologically vulnerable to patients' physical decline (compared to patients), and that caregiver ratings reflect their own internal experience rather than the patients' true abilities. For example, caregivers of patients with ALS appear to suffer emotionally (as evidenced by increased depression and perception of burden; Gauthier et al., 2007) and physically, as

patients become more incapacitated. Thus, caregiver ratings of patients' self-regulation could better reflect their own quality of life, which has been shown to decline as ALS progresses. Thus, the use of behaviorally specific measures may be most useful, especially when relying on caregiver reports.

In general, patients appeared to perceive more variability (i.e., lower inter-correlations) among self-regulatory abilities, such that self-regulatory deficits in one domain were not suggestive of deficits across other domains. This discrepancy across domains (i.e., social, thought process, emotions, cognitive) could be attributed to inaccurate perceptions of their condition. Alternatively, patients could be more flexible and realistic than caregivers in evaluating the specific deficits they experience. From a methodological standpoint, a lack of strong or significant correlations could be an artifact of the measures used. Although the scales used in this study generally had acceptable internal consistency, the construct validity of these measures as measures of self-regulation is not fully established. Interestingly, the measure that was most strongly and consistently related to other measures for both raters was the BRIEF-A, which was designed as a measure of global regulation of behavior across a variety of areas. It is possible that this measure best captures the variety of ways in which self-regulatory deficits are manifest. On the other hand, this measure did not highly correlate with measures of "cool" or "hot" EF. Thus, the idea that EF and SR draw upon a common resource but make unique contributions to behavior (Kaplan & Berman, 2010) is supported.

Taken together, there were few mean-level differences between patient and caregiver ratings, but there was a clear difference in the pattern of inter-correlations between raters across measures. Patient and caregiver agreement was highest when they rated the same individual (i.e., the patient) and more overt/observable behavior (e.g., emotional lability), and less when they expressed their own experience or rated the patients' internal experience (e.g.,

rumination). Of particular interest was the disagreement between patients and caregivers in perceptions of relationship cohesion. Given the tendency of caregivers to interpret patients' deficits as part of a pervasive pattern, and their susceptibility to decreased QOL, caregivers were expected to perceive less cohesion in their relationship. However, patients tended to perceive less cohesion. Patient-caregiver agreement was highest at the polar ends of the spectrum (at lower scores and at higher scores). Even more, the effect of good "cool" EF differed for patients and caregivers. For patients, good "cool" EF was associated with more cohesion, only if there was also good "hot" EF. For caregivers, however, the relationship between good "cool" EF and cohesion was strengthened by poor "hot" EF. Thus, the spectrum of impairment appears to vary both quantitatively (how much impairment) and qualitatively (what kind of impairment). Eliciting patient and caregiver reports may provide unique insights into the nature of the deficits as well as the psychological experience of the patient-caregiver dyads.

Is Self-Regulation Important for QOL?

A plethora of research has recently focused on QOL in ALS patients and their caregivers. Consequently, the current research aimed to examine patient-caregiver agreement regarding patients' self-regulatory capacity, and the contribution of these perceptions on quality of life. Previous literature consistently suggests that caregivers may be more "vulnerable" to the progression of ALS, generally rating poorer QOL over the course of the illness (Averill et al., 2007; Roach et al., 2009). However, caregiver QOL did not appear to be influenced by caregiver perceptions of patients' self-regulatory abilities. It is possible that the more global factors (e.g., progression of time and disease) are most important to caregiver QOL. Conversely, several domains of self-regulation were related to patient QOL. Rumination, lack of cohesion, and social anxiety were linked to worse QOL for patients.

Despite this evidence for the link between SR and QOL, research consistently suggests that patients generally maintain QOL over the course of their illness (Robbins, Simmons, Bremer, Walsh, & Fischer, 2001). In sum, although SR may be an important component of patients' QOL, there are likely other important factors contributing to or preserving well-being in ALS patients. Future research is needed to inform 1) the factors that contribute to declines in caregiver well-being and 2) the "protective" factors regarding patient well-being, and enhance interventions with ALS caregivers.

Are Physiological Resources Important?

This study lends support to the claim that glucose is an important component of successful self-regulation (Benton et al., 1994; Gailliot, 2008; Gailliot & Baumeister, 2008; Fairclough & Houston, 2004). Glycosolated hemoglobin (i.e., A1c) was significantly related to patient and caregiver perceptions of global regulation. Thus, patients with better regulated glucose were viewed and viewed themselves as more regulated on a global measure of self-regulation. Although non-significant, the general pattern that emerged was consistent with expectations across domains, such that lower (e.g., better) A1c values were associated with less emotional lability, less rumination, less social anxiety, and better "cool" and "hot" EF for both patients and caregivers. Thus, although a causal mechanism is not established, it is possible that measures reflective of glucose (tolerance or regulation) could serve to "mark" those patients who are also likely to experience self-regulatory deficits.

However, the current study only partially converges with research linking vagally-mediated HRV to prefrontal activity and SR (Brosschot et al., 2006; Thayer, 2007; Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Segerstrom & Solberg Nes, 2007). Higher resting HRV was associated with less emotional lability according to patients (but not caregivers), which converges with research linking emotional arousal to decreased (i.e., worse) HRV (Thayer et

al., 2009). Similarly, patient and caregiver ratings of patients' self-regulatory abilities across

other domains were consistently in the expected direction (albeit non-significant) with better

regulation linked to higher HRV. However, the pattern of associations among measures of EF

and HRV were unexpected, such that better "cool" EF was significantly associated with lower

(e.g., worse) baseline HRV in the current sample. A similar, non-significant pattern emerged

between "hot" EF and HRV. Taken together, this study suggests the mechanisms by which

HRV indexes the capacity for self-regulation in ALS patients may differ from other "healthy"

samples. If decreased HRV is in fact associated with the disease process of ALS (Oey et al.,

2002; Pisano et al., 1995), examining individual differences in HRV may be particularly

informative to self-regulatory processes. Alternatively, HRV could more dynamic in ALS

patients than in "healthy" samples (Sinnreich, Kark, Friedlander, Sapoznikov, & Luria, 1998),

which may suggest both theoretical and methodological adaptations for non-healthy samples.

Limitations

There are several limitations to the current research that should be acknowledged when

interpreting results and drawing conclusions. First, the sample of patients was both small and

varied. Although there was sufficient power to detect large effects, which had been previously

obtained in research on SR and EF, a larger sample would have increased the power to detect

small to moderate effects, which may be clinically important in ALS. Even more, a small

sample size necessitated careful selection of control variables to preserve degrees of freedom

in analyses (Breaugh, 2006; Lynam, Hoyle, & Newman, 2006; Segerstrom, 2009). A related

methodological concern is Type 1 error due to multiple comparisons. The current study did

not involve a correction (e.g., Bonferroni) for Type 1 error. Given the limited sample size, the

caution in relying on *p*-values in small samples, the risk of neglecting Type 2 error, and the

absence of theoretically guided a priori hypotheses (in many instances), preservation of power

was a priority. The sample was also heterogeneous with regard to the site of MND and disease onset. ALS and PLS patients were included in the sample given the similar conceptualizations of the disorders as MND. Despite the relationship between ALS and PLS, they clearly have different disease trajectories, with PLS progressing slower and being less fatal. Thus, it was important to identify any disease-related differences the groups with regard to demographics or variables of interest. This did not appear to influence the results of the current study, but there are likely differences with regard to treatment implications and survival. Methodological limitations should also be considered. To accommodate patients of varying functional levels, measures that could be administered independent of speech and mobility were selected. Therefore, the selection of measures was largely influenced by practical considerations with this population, which is a common concern in the assessment of individuals with ALS. Thus, it is possible that more valid or reliable measures (e.g., intelligence) would enhance confidence in the current results. However, given the similar patterns of inter-correlations among measures, it is unlikely that the substitution of any specific measure would substantially alter the conclusions of this research. However, the need to establish and validate appropriate assessment techniques for samples such as ALS patients (e.g., with limited mobility or communicative abilities) is important.

Overall, ALS patients appear to be prone to a variety of self-regulatory deficits, ranging from subtle to severe. However, this research suggests that both the quantity and quality of impairment varies, and that the correlates of these deficits may be different for patients and caregivers. However, adequate self-regulation across domains appears to influence quality of life for patients and caregivers.

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    protein positive neuronal and glial inclusions in ALS. *Neurology, 61,* 1766-1773.

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    standard tests of heart-rate variation in newly diagnosed IDDM patients. Diabetes Care,

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Zimmerman, E.K., Eslinger, P.J., Simmons, Z., & Barrett, A.M. (2007). Emotional perception

    deficits in amyotrophic lateral sclerosis. *Cognitive Behavior & Neurology, 20,* 79-81.

<center>**Vita**</center>

<center>**Abbey R. Roach**</center>

Place of Birth: New Albany, IN
Date of Birth: May 25, 1982

EDUCATION
University of Kentucky
B.A., Psychology, Summa Cum Laude   2000-2003

RESEARCH POSITIONS

University of Kentucky	"Thoughts, Stress, & Immunity in Older Adults"
Dept of Psychology	P.I.: S. Segerstrom, Ph.D.
Project Manager	

University of Kentucky	Nutrition and Noninvasive Positive Pressure Ventilation
Dept of Neurology	(NIPPV), Early Treatment in ALS"
Data Analyst	P.I.: E.J. Kasarskis, M.D., Ph.D.

University of Kentucky	"Anxiety, Depression, Optimism, and Cellular Immunity"
Dept of Psychology	P.I.: S. Segerstrom, Ph.D.
Interviewer	

Invited Reviewer	Journal of Personality and Social Psychology
	Personality and Individual Differences

RESEARCH PUBLICATIONS

Segerstrom, S.C., **Roach, A.R**., Evans, D.R., Schipper, L.J., & Darville, A.K. (in press). The structure and health correlates of trait repetitive thought in older adults. *Psychology and Aging.*

Roach, A., Averill, A., Segerstrom, S.C., & Kasarskis, E. (2009). The dynamics of quality of life in ALS patients and caregivers. *Annals of Behavioral Medicine,* 37(2), 197-206.

Roach, A.R., Lykins, E.L.B., Gochett, C.G., Brechting, E.H., Graue, L.O., & Andrykowski, M.A. (2009). Differences in cancer information seeking behavior, preferences, and awareness between cancer survivors and healthy controls: A national, population-based survey. *Journal of Cancer Education,* 24, 73-79.

Roach, A., Salt, C., & Segerstrom, S.C. (2009). Generalizability of repetitive thought: More a matter of degree than of kind. *Cognitive Therapy and Research*, 34, 144-158.

Solberg Nes, L., **Roach, A.R.**, Segerstrom, S.C. (2009). Executive function, self regulation, and chronic pain: A review. *Annals of Behavioral Medicine,* 37(2), 173-183.

McQueary, S., Schipper, L.J., **Roach, A.R**., & Segerstrom, S.C. (2009). Gender differences in delayed-type hypersensitivity response: Effects of stress and coping in first year law students. *Brain, Behavior, and Immunity,* 23(5), 672-676.

Lykins, E.L.B., Graue, L.O., Brechting, E.H., **Roach, A.R**., Gochett, C.G., & Andrykowski, M.A. (2008). Beliefs about cancer causations and prevention as a function of personal and family history of cancer: A national, population-based study. *PsychoOncology,* 17, 967-974.

Segerstrom, S.C., & **Roach, A**. (2007). On the physical health benefits of self-enhancement. In E.C. Chang (Ed.), *Self-Criticism and Self-Enhancement: Theory, Research, and Clinical Implications*. Washington, D.C.: American Psychological Association.

Solberg Nes, L., & **Roach, A.** (2006). Optimism/ Pessimism. In A. Hedblad, (Ed.), *International Encyclopedia for Social Sciences*, 2nd Ed, Farmington Hills: Thomson Gale.

RESEARCH PRESENTATIONS

Solberg Nes, L., **Roach, A.R**., Carlson, C. R., Crofford, L. J., Ehlers, S. L., Segerstrom, S. C. (2010) Self-Regulation, Executive Functions, and Chronic Pain. Symposium presentation at Social Neuroscience in Health Behavior and Health Communication symposium at Society for Behavioral Medicine, Annual Conference in Seattle, WA, April 7 – 10, 2010.

Roach, A.R., Salt, C., & Segerstrom, S.C. (2009, February). Generalizability of Repetitive Thought: Examining Stability in Thought Content and Process. Poster accepted for presentation at the annual meeting of the Society for Personality and Social Psychology, Tampa, FL.

Roach, A.R., Lykins, E.L.B., Gochett, C.G., Brechting, E.H., Graue, L.O., & Andrykowski, M.A. (2008, March). Differences in cancer information seeking behavior, preferences, and awareness between cancer survivors and healthy controls: A national, population-based survey. Poster presented at the annual meeting of the Society of Behavioral Medicine, San Diego, CA.

Roach, A.R., Salt, C.E., & Segerstrom, S.C. (2006, January). *Examining traits in repetitive thought dimensions*. Poster presented at the annual meeting of the Society of Personality and Social Psychology, Palm Springs, CA.

Roach, A.R., Averill, A., Segerstrom, S.C., & Kasarskis, E. (2007, March). *Quality of life in amyotrophic lateral sclerosis*. Poster presented at the annual meeting of the Society of Behavioral Medicine, Washington, D.C. (Meritorious Student Award).

Roach, A.R., Averill, A., Segerstrom, S.C., & Kasarskis, E. (2007, March). *Quality of life in amyotrophic lateral sclerosis*. Poster presented at the annual meeting of the Kentucky Psychological Association, Lexington ,KY.

Roach, A.R., & Segerstrom, S.C. (2007, May). *Neuroendocrine and immune effects of repetitive thought*. Poster presented at the annual meeting of the Psychoneuroimmunology Research Society, Arcachon, France.

Averill, A.J., Brown, E., **Roach, A.,** & Segerstrom, S.C. (2005, May). The Health Benefits of Forgiveness. Pamphlet displayed in downtown Louisville, KY, and published online in connection with Kentucky Psychological Association's mental health awareness campaign, Heads Up Kentucky!

PROFESSIONAL AFFILIATIONS

Society of Behavioral Medicine
American Psychosomatic Society
Psychoneuroimmunology Research Society
Society of Personality and social Psychology
Kentucky Psychological Association

CLINICAL POSITIONS

Federal Bureau of Prisons, FMC Lexington   *Psychology Pre-doctoral Internship*
2009-2010

Cardinal Hill Rehabilitation Hospital   *Psychology Intern, Brain Injury Unit*
2009

Federal Bureau of Prisons   *Psychology Intern, Atwood Camp*
2009-2010

University of Kentucky, Dept. of Psychiatry   *Psychology Intern*
2006-2008

Kentucky Clinic, Dept. of Family Medicine   *Psychology Intern*
2005-2006

Harcourt Assessment, Inc.   *Field Examiner*
2006-2008

Harris Psychological Services Center   *Therapist*
2005-2008

Maryhurst, Inc.   *Youth Counselor*
2004

Eastern State Hospital   *Mental Health Associate*
2003

HONORS AND AWARDS

Harris Dissertation Award	2009
American Psychosomatic Society Citation Poster Award	2009

Society of Behavioral Medicine Meritorious Student Award	2007
Commonwealth Research Award	2007
Charles T. Wethington Fellowship	2004-2005
U of K Arts and Sciences Cleveland Scholarship	2003
University of Kentucky Academic Excellence Scholarship	2002
American Legion/ Ladies Auxiliary Academic Scholarship	2001-2003
Emerson Electric Scholarship	2000-2003
Dean's List	2000-2003
University of Kentucky Honors Program	2000-2003
Kentucky Governor's Scholar, Centre College	1999