HEMISPHERIC AND EXECUTIVE INFLUENCES ON LOW-LEVEL LANGUAGE PROCESSING AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) has great impact, both to public health as well as to the individuals who sustain one. Some of the most problematic deficits after TBI arise in cognitive areas like executive functioning and language. Language deficits at the level of discourse are commonly reported (e.g., Snow, et al., 1998), but evidence of lower-level language problems has been more scarce. One possible explanation for that pattern of findings (e.g., McDonald, 1992) is that underlying executive deficits are responsible for the discourse problems. A goal of the current studies is to see, then, what effect variations in executive demands have on lower-level language after TBI. A second goal is to begin to examine mechanisms for those processing differences. The most common neuropathology after TBI is diffuse axonal injury (DAI), which has been estimated to be present in a large percentage of cases, and commonly affects the corpus callosum (Pittella & Gusmão, 2004). Based on these facts, it was hypothesized that altered interhemispheric communication might be involved in the cognition problems faced by people with TBI. To examine the effects of hemispheric communication and executive demands on language processing after TBI, two behavioral experiments using split visual hemifield presentation and one functional connectivity analysis of resting-state fMRI data were conducted.

The task in the first experiment was semantic priming with lexical decision. As compared to controls, participants with TBI showed a stronger right visual field (RVF) advantage and selective impairments suggestive that language was primarily affected when executive demands were higher. The second experiment confirmed these results with a verb generation task collecting vocal latencies (from Chiarello, et al., 2006). Finally, the functional connectivity analysis compared connectivity values between right and left hemisphere areas thought to be involved in language and executive functioning. This analysis, while preliminary, provided some evidence suggesting that persons with TBI may have higher functional connectivity at rest than matched controls, especially for right hemisphere connections and links to anterior cingulate cortex. Together these findings begin to reveal a complex picture where hemispheric and executive factors have important bearing upon language processing in people with TBI.

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PREFACE

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1.0 INTRODUCTION

1.1 BACKGROUND: TRAUMATIC BRAIN INJURY

1.1.1 Definition

Traumatic Brain Injury (TBI) is defined by the TBI Model Systems National Database (Harrison-Felix, Newton, Hall, & Kreutzer, 1996:2) as: "(D)amage to brain tissue caused by an external mechanical force, as evidenced by loss of consciousness due to brain trauma, post-traumatic amnesia, skull fracture, or objective neurological findings that can reasonably be attributed to TBI on physical examination or mental status examination." Other definitions further emphasize the mechanisms of injury, e.g., "craniocerebral trauma, specifically an occurrence of injury to the head arising from blunt or penetrating trauma or acceleration/deceleration forces" (Thurman, Coronado, & Selassie, 2007:45). In other words, the formal definitions of TBI are in line with the layperson's interpretation of the name: TBI is a general term for any sort of traumatic injury to the brain. While the nature of the resulting damage to the brain can cover a wide range, the definitions stress the origin of the injury because there are similar features to the kinds of damage that can result.

1.1.2 Methods of Injury

The three most common methods of sustaining a TBI include motor vehicle accidents (car, motorcycle, and other vehicles like ATVs), falls, and assaults (Langlois, Rutland-Brown, & Thomas, 2006). In all of these, there are only two possible types of situations that can arise with respect to the head and its surroundings (Yeates, 2000). In the first, less common situation, a moving object strikes a stationary head. This state of affairs is called impression, and of the categories listed above, only certain types of assaults tend to fall under this category. Acceleration/deceleration injuries are far more common and they arise when a moving head impacts a stationary object (Trimble, 1990). Depending how the head strikes the object, translational and/or rotational type complications can result. Purely translational injuries come about when there is linear acceleration through the head's center axis. Rotational injuries arise when the axis of movement is not directly in the center of the head, such that when the skull is stopped the brain keeps moving. These types of injuries have certain characteristic features that will be discussed below.

1.1.3 Demographics

TBI does not affect all groups of people equally. The two peak age ranges for TBI are 15-24 and > 75 years of age (Ricker, 2009). Men are affected 2-3 times more than women (McAllister, 1992; Ricker, 2009). A number of pre-injury factors have been shown to co-occur with TBI, including learning disabilities, alcohol or drug abuse, violence or criminal history, emotional problems, and attention deficits (Ricker, 2009), although not much is known beyond correlational tendencies. Factors like these also correlate with return to work after TBI, with age at time of injury and pre-injury occupation/education being two of the major determining factors along with injury severity (see Keyser-Marcus, Bricout, Wehman, Campbell, Cifu, & Englander, 2002; or Wehman, Targett, West, & Kregel, 2005; for reviews).

1.1.4 Incidence and Impact

Traumatic Brain Injury (TBI) has been called the silent epidemic (Langlois et al., 2006). It is estimated that TBI affects at least 1.4 million people a year (CDC, 2001; accessed from http://www.cdc.gov). There is a high occurrence of death that results from traumatic brain injury as well as disability (5.3 million people may be living with disability from a TBI at any time, Katz, Zasler, & Zafonte, 2007). The public health impact is thus very great, with both incidence and lifetime cost for care quite high. The estimated lifetime cost for TBIs sustained in 1995 reached $56.3 billion, and although the annual incidence of TBI is several times greater than spinal cord injury, HIV/AIDS, or even breast cancer (Thurman et al., 2007), most people remain largely uninformed about this public health threat. For the individuals affected by TBI, however, it can have enormous impact because of the nature of the injury as well as the consequences that result.

1.1.5 Resulting Sequelae

While it seems like a traumatic brain injury could potentially lead to any type of damage, there tend to be commonalities among TBIs both in terms of the injury to the brain as well as the resulting physical, psychological, and cognitive sequelae. These commonalities arise because of the way the brain is formed and the physical action upon it, which frequently occurs with TBI (i.e., the effect of inertial loading and accelerative and decelerative forces).

1.1.5.1 The Injury To The Brain

1.1.5.1.1 Coup/Contre-coup and Focal Lesions

Focal lesions are relatively rare after TBI, and tend to be caused by impression-type injuries. To the extent that focal lesions occur, they tend to disproportionately affect the frontal lobe as well as portions of the temporal lobe. This outcome is generally thought to occur because those lobes rest in close proximity to bony protrusions in the skull (Alexander, 1995; Callon & Jackson, 1995; Levin & Kraus, 1994; Trimble, 1990). If there is a focal lesion at the site of impact, it is known as a *coup* injury. *Contre-coup* injuries are those that take place across the head from the coup injury, when the brain is pushed and impacts the other side of the skull. A more common outcome from TBI, however, is actually multifocal microlesions, described below.

1.1.5.1.2 Diffuse Axonal Injury and Secondary Mechanisms

More notable than focal lesions in TBI is the traumatic injury to axons that results from combined forces (impact, acceleration and/or deceleration). Alexander (1995) and others describe this as the primary neuropathology in TBI, and it is associated with deficits in cognitive functioning (e.g., Scheid, Walther, Guthke, Preul, & von Cramon, 2006). What results from this kind of injury are microscopic lesions affecting the fiber tracts which connect various areas of the brain. These are largely found in the cerebral cortex and minimally affect brainstem areas (Callon & Jackson, 1995). Because of the vast interconnectedness of the frontal lobes (e.g., Goldberg, 2001), this injury may also have a preferential impact on the frontal lobes via white matter disconnection.

Diffuse axonal injury (DAI) is the name given to the damage done by TBI which does not involve large focal lesions. It is also sometimes referred to as traumatic axonal injury (TAI)—a moniker which sidesteps the problem that this injury is not actually diffuse, but rather multifocal, with common sites of occurrence found in multiple studies. Most frequently affected are the corpus callosum and the dorsolateral part of the midbrain (e.g., LeClercq, McKenzie, Graham, & Gentleman, 2001). A tiered grading system set forth by Adams and Gennarelli and colleagues describes a grade 1 injury as affecting the hemispheric white matter, a grade 2 as having additional involvement of the corpus callosum, and a grade 3 as showing additional lesions in the superior cerebellar peduncle (Adams, Doyle, Ford, Gennarelli, Graham, & Mclellan, 1989; Gennarelli, Thibault, Adams, Graham, Thompson, & Marcincin, 1982). In an experimental study with monkeys subjected to rotational forces, the most common result was a grade 3 injury—suggesting that the corpus callosum is often affected by DAI. These common anatomical foci are the product of the physics of the injurious force applied to a structure that has areas that are more free to move (the cerebral hemispheres) attached to areas that are less free to move (midline and interhemispheric areas). It is near these junctions where DAI primarily occurs.

DAI is an injury which is generally thought to arise from certain types of TBIs—most commonly, those that involve accelerative and decelerative forces. Although it gets described as a shearing injury it is likely that most of the damage is secondary to the initial stretching. The initial part of the cascade that follows is still being debated, but it is believed that there is a change in the permeability of the axonal membrane due to a dysregulation of calcium. What results is an impairment in axonal transport (Povlishock, 2008). Evidence has also been found for both necrotic and apoptotic cell death resulting from DAI (Raghupathi, 2004). These seem to be more due to the mechanical disruption to the cell's body and membrane (Povlishock, 2008).

These microscopic lesions are difficult to detect. Studies over the years have advocated different imaging methods to improve identification of DAI—beginning with the standard computed tomography (CT), and moving to general magnetic resonance imaging, or MRI (e.g., Parizel et al., 1998; Tomaiuolo et al., 2005), special sequences of MRI (Takaoka et al., 2002), and finally Diffusion Tensor Imaging (DTI, Ezaki, Tsutsumi, Morikawa, & Nagata, 2006). Each imaging method has been beneficial in improving the number of cases of DAI diagnosed clinically, but still the only definitive diagnostic for DAI is microscopic (Kraus, Susmaras, Caughlin, Walker, Sweeney, & Little, 2007), and autopsy studies in TBI have suggested that DAI is massively underdiagnosed. One autopsy study surveying 122 brains with DAI found that 55 of those required microscopic study to determine DAI diagnosis and/or severity (Adams et al., 1989). Another, which examined 120 brains of people who died in road traffic accidents found evidence of DAI in 80% of those brains on autopsy. This figure included 22% at Grade 1, 51% at Grade 2, and 27% at Grade 3 (Pittella & Gusmão, 2004). Confusing the issue is the fact that clinicians sometimes give a diagnosis of DAI when all evidence of focal lesions has been ruled out but the patient still exhibits symptoms of a more severe brain injury. When DAI is given as a diagnosis based on scan findings, it is often due to the appearance of petechial hemorrhages. These microbleeds are associated with DAI, but perhaps only with the more severe form. These discrepant diagnostic criteria suggest that DAI is not yet a standardized diagnosis. Based on the autopsy studies, however, it seems likely that a high percentage of persons who have experienced TBI do in fact have resulting DAI, and a high percentage of those likely have damage in or around the corpus callosum.

1.1.5.2 Whole Person Disturbances

What happens physically and chemically in the brain can result in an abundance of sequelae in various spheres of life—people who have experienced a traumatic brain injury can find themselves impacted physically, psychologically, cognitively and in just about every way imaginable.

1.1.5.2.1 Physical and Psychological Disturbances

Physical complications after TBI arise from damage locally (e.g., if there is brainstem involvement) as well as secondary cascades of hormones and other chemicals. Immediately after injury there may be coma and/or posttraumatic amnesia, both of which may be related to the amount of DAI present (Gennarelli, 1993). There are few systems that are unaffected by TBI—changes can occur in cardiovascular, respiratory, metabolic, musculoskeletal, gastrointestinal, genitourinary, hematologic, dermatologic, and autonomic systems (Callon & Jackson, 1995; Gennarelli, Thibault, Adams, Graham, Thompson, & Marcincin, 1982). Seizures may occur, and persons with TBI may experience such symptoms as fatigue, irritability, loss of temper control, depression, headache, dizziness, and problems with mood (McAllister, 1992).

1.1.5.2.2 Cognitive Disturbances

Traumatic brain injury can have a great impact on cognitive function even when symptoms seem relatively mild. While there are differences between individuals, problems with memory are the most commonly described cognitive sequela after TBI (Raskin, 2000), but executive functioning (including working memory and attention), speed of processing, and language can all be affected as well. Several researchers have found that multiple aspects of cognition (including various forms of memory, attention, speech and communication factors) are important in predicting return to work (Cattelani, Tanzi, Lombardi, & Mazzucchi, 2002; Drake, Gray, Yoder, Pramuka, & Llewellyn, 2000; Isaki & Turkstra, 2000).

1.1.5.2.2.1 Memory

Memory is the cognitive domain most commonly mentioned as problematic after traumatic brain injury (Raskin, 2000). This is especially true of self-reports (Raskin, 2000), but memory deficits have been observed for almost every type of memory, even though most people with TBI would not be considered traditionally amnestic once their periods of post-traumatic amnesia have resolved. Modality, time of delay, learning and forgetting rates, and almost any other variable relevant to memory study have been shown in the literature to cause problems for persons with TBI (see Vakil, 2005, for a review). Prospective memory function is also affected, and has been found to be most closely related to self-report scores (Kinsella et al., 1996). Pilolino and colleagues even found evidence that episodic autobiographical memory recall is significantly impaired in persons who experienced a severe TBI as compared to controls, a finding that was unrelated to the distance of the memory from the testing time or the person's age (Pilolino, Desgranges, Manning, North, Jokic, & Eustache, 2007). Studies employing measures of brain activation further suggest that there is differential recruitment of brain areas for persons with TBI, especially during free recall (e.g., Ricker, Müller, Zafonte, Black, Millis, & Chugani, 2001).

Given the diverse findings, characterizing the nature of the memory deficit is difficult, as there is evidence for differences in learning and the encoding process, as well as in the retrieval of information from short- or long-term storage. Work on subgroups of memory functioning might suggest that these results are indicative of different patterns of responding (Curtiss, Vanderploeg, Spencer, & Salazar, 2001). Other researchers, however, have noted that memory deficits often go hand-in-hand with deficits of executive functioning, and have begun to implicate the latter as a cause for the former (as discussed in Raskin, 2000).

1.1.5.2.2.2 Executive Functioning

Executive control or executive functioning are blanket terms for a number of related processes associated with the ability to regulate and/or control other processes or behaviors. Different researchers have touched upon different functions as providing the crux of executive functioning, including such things as planning, attention, fluency, etc. Regardless of how executive functioning is defined, it is one of the major cognitive areas in which persons with TBI have difficulty. As will be reviewed in more detail below (see section 1.4), evidence is seen for executive difficulty in almost all studies examining it—including those using neuropsychological tests, rating scales, and even neuroimaging methods. A deficit that might be related to this is difficulty with speed of processing.

1.1.5.2.2.3 Speed of Processing

Another common cognitive finding after TBI is a speed of processing deficit (see Matthias et al., 2004, for a review). While this is often reported as a response time difference between persons with TBI and control participants, it is not attributable to simple motor factors, as it can occur even when simple motor response times are statistically identical between TBI and control groups (Russell, Scanlon, Arenth, & Ricker, 2009). Speed of processing differences have been noted during verbal and visual fluency, verbal memory, serial addition, and many other tasks (e.g., Bittner & Crowe, 2007; Madigan, DeLuca, Diamond, Tramontano, & Averill, 2000; Mathias et al., 2004). It seems that tasks which are more cognitively "complex" or require interhemispheric transfer are most likely to elicit speed of processing difference effects. Cognitively or physiologically, however, the exact causes of such findings are still unclear. What gets described as a speed of processing deficit may in fact be due to executive dysfunction, hemispheric disconnection, or a combination of these factors. More study in this area, especially with temporally sensitive techniques like ERP, is necessary to tease these possibilities apart.

1.1.5.2.2.4 Language

One final cognitive area in which complaints are heard is language. Historically, researchers have had varied opinions on whether or not people with TBI have language problems. Given that the original studies typically relied on aphasia batteries as the sole form of language evaluation, it is not surprising that language after TBI has been described as not affected, or non-aphasic. This finding is largely a result of the test batteries used—many aphasia batteries are meant to assess basic language functioning, and they often do not look at language higher than the level of the simple sentence, thus potentially underrepresenting impairments in non-stroke populations (Chapman, Levin, & Culhane, 1995). The observations of clinicians were in direct contrast to these results—they report that communication with these people is often difficult. The general feeling reported was that, in the face of little or no deficit found during testing, people with TBI could exhibit marked problems when having a communication, though these problems were not well described (Hagen, 1984; Hinchliffe, Murdoch, & Chenery, 1998).

If there is a current consensus in the literature, it is that the language problems people with TBI have are higher-level language problems—most evident at the level of discourse or narrative. Many researchers (e.g., Kaczmarek, 1987; McDonald, 1992; Ylvisaker & Szekeres, 1989) also believe that the communication deficits may result from underlying cognitive deficits, but the link between the two has not been well studied. There has been a recent focus on discourse processing as the main communication difficulty after TBI (Body & Perkins, 2004). At the level of discourse, it is reasonably easy to imagine that other cognitive processes could be interacting with language such that their impairment could be leading to language impairments. What has been overlooked, however, is that language problems after TBI are not limited to the discourse level, as the current review will now demonstrate. Instead of only one, there are at least three levels at which people with TBI can be seen to exhibit difficulty.

1.2 LANGUAGE AFTER TRAUMATIC BRAIN INJURY

First, given that much of the recent focus in the literature has been on discourse, it is important to review studies dealing with discourse. Sentence-level language has not been well studied, and what few reports there are have been conflicting, but it seems clear that there is evidence of sentence-level language problems, and this will be the second area discussed. Finally, multiple reports have been made of problems with naming and verbal fluency, so findings regarding single word processing will be reviewed.

1.2.1 Discourse Level Language

As mentioned above, the discourse level is the current focus of research on language deficits in TBI (Body & Perkins, 2004), and is often investigated with conversational samples or narratives. The discourse problems recounted by researchers are varied, but can be grouped into three main types of problems: giving information, structuring, and inferencing.

The deficits with information giving are quite exhaustive. They can include the amount of information given (generally too little), structuring of the information given, and the kind of information given—problems arise both in providing the essential information, and also in excluding information that is not necessary (Coelho, 2007). The amount of information given has been studied in a number of ways, and has been counted either by looking at the number of propositions produced or by considering the total number of comments made. While there is not a consensus in the literature regarding the relative amount of speech used by people with TBI, the amount of necessary information given is generally found to be less. Coelho, Youse, & Le (2002), analyzing conversations between brain-injured and non-brain-injured adults and an experimenter, found that the TBI group made fewer comments overall, but that they were equal to normal controls in the number of turns made, and the number of topics initiated. While not finding a difference between people with TBI and controls on the total number of utterances or the total duration of speech during conversation, Snow, Douglas, & Ponsford (1998), did find that people with TBI gave insufficient information. McDonald & Pearce (1995) also found no difference in total number of propositions given by people with TBI and controls. McDonald (1993; McDonald & Pearce, 1995) reports that people with TBI gave more "extra" propositions—i.e., providing unnecessary or extraneous information while perhaps sacrificing essential information. Besides irrelevant information, the narratives of people with TBI have been characterized as having unnecessary repetitions (McDonald, 1993; Snow et al., 1998) as well as inaccuracies (Snow et al., 1998; Tucker & Hanlon, 1998). Together, these results suggest that, when in conversation or providing a narrative, people with TBI tend to give inaccurate, redundant, or irrelevant information, sometimes at the expense of the essential propositions.

When correct propositions are given, the ordering of them also tends to be problematic. Deficits have been reported in global structuring of narratives, in sequencing of propositions within a narrative, and in maintenance of topic throughout. All of these skills contribute to the overall comprehensibility of the narrative. Lack of global structure in particular leads to lower coherence. Hough & Barrow (2003) found that, relative to controls, their TBI participants' narratives were given lower coherence ratings due to reduced global structure. Sequencing of individual propositions also contributes to a sense of coherence within a narrative. Several authors have noted difficulties with proposition sequencing in people with TBI (McDonald, 1993; McDonald & Pearce, 1995; Snow et al., 1998).

The above discussion has focused on production, but problematic comprehension of language above the sentence level has also been noted. The major focus of such work has been inferencing. During normal conversation or storytelling, much goes unsaid. It is up to the listener to piece together what is unstated but necessary for understanding. Several groups have reported that inferencing is difficult for people with TBI. Hinchliffe et al. (1998) found that their TBI group was significantly impaired relative to controls on a test of inference-making. A knowledge-based inferencing task constructed by Barnes & Dennis (2001) led to similar results. Despite similar rates of acquisition and retention of the knowledge base by their control and non-control participants, they found that people with TBI had lower rates of inferencing. Finally, pragmatic inferencing has also been found to be problematic for people with TBI, whether it is tested by having participants make judgments about responses one character makes in a vignette (Channon & Watts, 2003), or seeing how participants respond to various conversational implicatures and presuppositions (Dennis & Barnes, 2000). Based on the previous paragraphs, it seems there is good reason to believe that discourse can be a problem after TBI. The literature on sentence-level language is less clear.

1.2.2 Sentence Level Language

Language at the sentence level in TBI has been considered relatively intact, and while multiple kinds of sentence level deficits have been reported, in both expressive and receptive language, these tend to be restricted to non-adult populations or adults just after injury. Production deficits that have been described range from repetition of sentences in newly-injured adults (Payne-Johnson, 1986) to construction of sentences under different conditions, by children and adolescents (Chapman et al., 2004; Dennis & Barnes, 1990) and adults still in the hospital for the TBI (Payne-Johnson, 1986). One study including sentence-level tests in adults slightly farther from injury (M = 4 months; Hinchliffe et al., 1998) reported no group differences between people with TBI and controls on sentence repetition and sentence construction (though the latter was rejected based on a marginal p-value of 0.052).

Comprehension deficits found include problems in reading or listening to sentences, as well as more specific trouble with processing sentential semantics and syntax. These deficits do not seem to limit themselves to children or adults with new-onset TBI, but are also found in people with TBI in later stages of recovery in what few studies do exist in the literature. Hinchliffe et al. (1998) has shown poorer performance on reading comprehension of sentences, as well as ambiguous sentences and sentence comprehension tasks hinging on semantic features. Butler-Hinz, Caplan, & Waters (1990) found syntactic comprehension deficits in persons with TBI similar to those found in their group with left hemisphere stroke. These two studies, however, make up the bulk of the research on this area, suggesting that more work is necessary before it can be seen definitively what, if any, sentence level language deficits are common after traumatic brain injury. With the information currently available, it seems most likely that for chronic-stage adults, sentence level language is relatively intact. It is also important, however, to examine lower-level deficits in language processing.

1.2.3 Word Level Language

Three main problems have been described at the word level: naming and word-finding, fluency, and difficulty with lexical semantics. Naming has been studied using a number of different kinds of tasks, including subtests from various neuropsychological tests as well as more nonstandard assessments. Naming was originally thought to be the major language problem in TBI (Heilman, Safran, & Geschwind, 1971; as discussed in Levin, Grossman, Sarwar, & Meyers, 1981), and object naming is still thought of as one of the most common language deficits after TBI (Bittner & Crowe, 2006). Payne-Johnson (1986) used naming subtests of the Boston Diagnostic Aphasia Examination (BDAE—Goodglass & Kaplan, 1983) including Animal Naming and Confrontation Naming. People hospitalized in the acute phase of TBI were found to do less well on these tests than non-neurologic hospital patients. While naming difficulties can clearly be seen in the acute phase, these findings have also been noted later. Hinchliffe et al. (1998) have noted similar naming deficits relative to normal controls using the Boston Naming Test (BNT—Kaplan, Goodglass, & Weintraub, 1983), and the naming subtest of the Western Aphasia Battery

(WAB—Kertesz, 1982) with people with TBI 2-12 months post-injury. Modality also does not seem to matter, as Levin and colleagues (Levin et al., 1981) found deficits in a large number of their participants with TBI who were 6 or more months post-injury in both visual picture naming and haptic naming. Raskin, Mateer, & Tweeter (1998), found naming deficits even in people with mild TBI a mean of 21.75 months post-injury using the Picture Rapid Naming Test. The idea that naming deficits continue past the acute stage of TBI has also been supported by clinical observation (Chapman et al., 1995).

Naming is not the only word-level deficit, however. A number of researchers have noted a decrease in verbal fluency among people with TBI. All of these studies have used the Controlled Oral Word Association Test (COWAT—Benton & Hamsher, 1976), a test which is often used to measure executive functioning, but is also used as a language measure occasionally. In the COWAT, a person is asked to generate words, often words starting with a given letter or category. Reports of 17-19% of the TBI group tested being impaired on this have come from a few sources (Bittner & Crowe, 2006; Levin et al., 1981; Raskin et al., 1998). It has also been reported that performance of the COWAT gets worse in groups having suffered a more severe injury (Catroppa & Anderson, 2004). Finally, when performance of people with TBI is compared to controls, the controls do significantly better on the COWAT (Hinchliffe et al., 1998).

Issues of lexical semantics have also been found to be problematic for people with TBI. Using several subtests of The Word Test—Revised (TWT-R—Huisingh, Barnett, Zachman, Blogden, & Orman, 1990), Hinchliffe et al. (1998) demonstrated deficits on a number of lexical semantic tasks. People with TBI were worse at generating definitions, synonyms, and antonyms for a given word, and also had difficulty choosing the unrelated word out of a group of four.

Together these results suggest that under some conditions there can be low level language deficits—and this is especially evident in verbal fluency situations.

1.2.4 Open Questions

While many researchers have recently been focusing on discourse level processing after TBI, the preceding review showed that there is evidence for language difficulty at other levels of language under certain circumstances. For instance, sentence comprehension and word processing problems may exist, as well. There are a few questions that arise from this review. First, why are the reports on language processing at the sentence and word levels so divergent? A review of the literature leaves one unclear as to what kind of language problems typically arise after TBI, and if low-level language is often affected, or only acutely. From the discourse investigations it seems that executive control is a possible influence on language problems, but studies do not address whether control can influence language at other levels, how widespread this influence might be (i.e., are all language difficulties simply due to executive dysfunction), or under what circumstances we might expect executive functioning to influence language. It is to these questions that we now turn.

1.3 INTERPLAY BETWEEN EXECUTIVE FUNCTIONS AND LANGUAGE

1.3.1 Models of executive functioning

Different researchers have touched upon various subskills as providing the crux of executive functioning. Knight & D'Esposito (2003) have described it as having three components: 1) focused and sustained attention, 2) fluency/flexibility/generation of novel situations, and 3) planning and regulation of behavior. McDonald, Flashman, & Saykin (2002), while also stressing planning, mental flexibility, and attention, add reasoning, concept formation, and purposeful behavior to their definition. Smith & Jonides (1999) cite task management and selective attention as the crucial skills. A model by Cohen and colleagues (e.g., Miller & Cohen, 2001) describes executive control as a biasing signal. Different definitions do not seem inaccurate, but most definitions seem rather incomplete, or nonspecific. This way of defining, however, is most likely necessary given the vast complexity of executive control processes, as well as the limitations in the ways they have been tested.

1.3.2 How might executive functioning be instantiated in the brain?

While researchers have long stressed the frontal lobes' role in executive behavior (e.g., Stuss & Alexander, 2000), the emerging picture is that brain instantiation for these skills may be much more complex and distributed. Different parts of the network may be attributed with being responsible for various subtasks of executive functioning in a way that is dependent on the task a particular research group uses, though. There is evidence for involvement of the cerebellum (Bellebaum & Daum, 2007) as well as other non-cortical structures like the basal ganglia (Casey, Tottenham, & Fossella, 2002; Heyder, Suchan, & Daum, 2004), but researchers who focus on cortical structures seem to be converging on a few key areas. Prefrontal cortex, especially right dorsolateral prefrontal cortex (DLPFC), gets extensive mention, as has anterior cingulate cortex (ACC, Cole & Schneider, 2007; Fassbender et al., 2006; Fassbender et al., 2004; Garavan, Ross, Murphy, Rocke, & Stein, 2002). The former tends to be implicated in inhibitory processes while the latter is often thought to be involved in error monitoring, sometimes along with the pre-supplementary motor area (preSMA). Parietal cortex is sometimes mentioned as well, though descriptions vary from inferior (Fassbender et al., 2006; Fassbender et al., 2004; Garavan, Ross, & Stein, 1999) to posterior (Cole & Schneider, 2007). Anterior insula has also been seen (Cole & Schneider, 2007; Garavan et al., 1999). While the extent of the network supporting executive functions still is not definitively elucidated, there is strong support for seeing it as distributed and extensive. Being so extensive in brain representation, it might be reasonable to posit that it would have an impact on other cognitive functions as well.

1.3.3 How might executive functioning influence language behavior in controls?

This question is one which has not received much attention, at least among non-patient populations. What studies have been done tend to look at the influence of working memory on language processing. Although digit span tasks have been widely used, a review by Daneman & Merikle (1996) suggests that comprehension is better predicted by tasks that tap both the storage and processing elements of working memory. This predictive power was not limited to verbal tasks, however, but was also seen in mathematics tasks with similar demands. While this line of research presents an interesting beginning, the question of how executive functioning might influence language is just starting to be addressed. This question may be interesting not only for cognitive modeling of these two skills; it also would have benefit for the literature on individual differences in cognition. The majority of work in this area, however, has been on people with more broad differences—people with some injury or syndrome affecting their cognitive functioning. This is especially true with traumatic brain injury. For that reason, it is to the literature on TBI and executive control that we now turn.

1.4 EXECUTIVE FUNCTIONING AFTER TRAUMATIC BRAIN INJURY

Now that some review has been made of executive functioning and how it might be instantiated in the non-injured brain, it is important to consider how injury might change the situation. In order to do this, it will be helpful to begin with a more in-depth discussion of performance on tasks of executive functioning, including findings from neuroimaging studies. Evidence of language and executive functioning interplay will then be reviewed.

1.4.1 How do people with TBI perform on tasks of executive functioning?

1.4.1.1 Behavioral Findings

While many studies have compared performance in people with TBI and controls, researchers have not typically looked beyond a general tendency for the former to be impaired relative to controls on measures of executive functioning. Self-ratings or ratings done by close others consistently report deficits of executive functioning (e.g., Channon & Watts, 2003; Coolidge & Griego, 1995; Proctor, Wilson, Sanchez, & Wesley, 2000). Impaired performance has also been noted using several kinds of tests including more traditional neuropsychological tests as well as newer, less structured tests and neuroimaging methods.

Traditional tests that have been used include the COWAT (described above), the Wisconsin Card-Sorting Task (WCST, Grant & Berg, 1948; Milner, 1963), the Stroop paradigm (Stroop, 1935), and the Trail-Making tests (TMT—A& B, Army Individual Test Battery, 1944) to name only a few. The results have not shown overwhelming evidence of impairment, though most results are suggestive of it. The WCST requires reasoning and concept formation as well as the ability to change mental set and inhibit old, now incorrect responses. Most researchers, however, have not found people with TBI to be impaired at this task (Hinchliffe et al., 1998; McDowell, White, & D'Esposito, 1997; Raskin et al., 1998; Raskin & Rearick, 1996, but c.f. Martzke, Swan, & Varney, 1991), but it seems to be the exception. Some researchers have found that people with TBI are even more impaired on inhibition of a dominant response in the Stroop task than controls (Hinchliffe et al., 1998; Raskin et al., 1998; Schmitter-Edgecombe & Wright, 2004). The Trail-Making tests involve drawing a line connecting a sequence of circled numbers on paper (TMT-A) or connecting alternating numbers and letters (TMT-B, e.g., 1-A-2-B, etc.). Trails A likely involves sequencing and concentration processes, while Trails B is thought to require additional set-shifting abilities (Korrte, Horner, & Windham, 2002). The general finding is that people with TBI are impaired on these tasks relative to controls (Brooks, Fos, Greve, & Hammond, 1999; Hinchliffe et al., 1998; McDowell et al., 1997; Raskin et al., 1998; Spikman, Deelman, & van Zomeren, 2000).

Looking at performance in dual- or multi-tasking situations is also commonly done, as it taps into such processes as sharing attention and task switching. Using dual tasking conditions combining visual reactions with either concurrent articulation or digit span, McDowell et al.,

(1997) found that people with TBI showed greater decrements in performance in dual-task conditions than did controls. Another study found that on both the Six Elements test (from the BADS battery, Wilson, Alderman, Burgess, Emslie, & Evans, 1996) and the Telephone Search while Counting (from the Test of Everyday Attention, Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996), the TBI group performed significantly worse than controls (Channon & Watts, 2003).

One problem with many of these standard tests is that even though they are meant to capture deficits that occur in unstructured situations, they are themselves structured. Some researchers have argued that the structured nature of standardized tests yields an underreporting of executive control deficits (Lezak, 1982). Newer tests designed to get around these problems include the Tinkertoy Test, in which a person is given 50 pieces of Tinkertoys and asked to build whatever they want (TTT, described in Lezak, Howieson, Loring, Hannay, & Fischer, 2004), and the Executive Function Route-Finding Task, which asks people to find their way to a location one or more floors and at least 5 choice points away (EFRT, Boyd & Sautter, 1993). Studies which have used these tests with people who have TBI have found them to be impaired relative to controls (Bayless, Varney, & Roberts, 1989; Martzke et al., 1991; Spikman et al., 2000).

1.4.1.2 Imaging Findings

Another way of looking at executive functioning after traumatic brain injury is with neuroimaging. McAllister and colleagues (McAllister et al., 1999; McAllister, Sparling, Flashman, Guerin, Mamourian, & Saykin, 2001) looked at performance on the N-back task in people who had sustained mild TBIs and found that, despite equivalent task performance, persons with mild TBI differed from control participants in their failure to increase activation in working memory areas steadily with increases in cognitive load. Differences in activation from controls on the N-back were also found for people with more severe injuries (Perlstein et al., 2004). One fMRI study which compared one brain-damaged participant to one control found greater increases in frontal activation during a task of inhibition in the person with TBI relative to the control, perhaps suggesting inhibition required more cognitive work (Scheibel et al., 2003). Differences in lateralization and dispersion of brain activation during executive tasks have also been seen between people with TBI and controls (Christodoulou et al., 2001; Newsome et al., 2007; Turner & Levine, 2008). In many of the cited studies, there is more right hemisphere activation found in the TBI group. One final study found larger foci of activation in the same areas as well as recruitment of additional areas for people with TBI as compared to controls when doing another executive task (Rasmussen, Antonsen, Berntsen, Xu, Lagopoulous, & Håberg, 2006). While these studies use different tasks and have somewhat different findings, what is consistent between all of these is the result that people with TBI are showing brain activation that differs from controls—usually showing more intense or more widely distributed activation, and especially more involvement of the right hemisphere. From all testing methods then, whether it be formal or more informal neuropsychological examination or even neuroimaging, it seems that there are clear findings of executive deficits after TBI. What remains to be investigated is whether there is evidence that these executive deficits could be impacting language processing.

1.4.1.3 Evidence of crossover

The idea of executive functioning deficits contributing to language problems is not completely novel, and there are some works in the literature providing supportive evidence. Three different types of evidence can be found—anatomical arguments, empirical studies, and rehabilitation findings. From the perspective of anatomy, the argument in support of an interface between language and executive functioning is simple: there is overlap in areas thought to be involved in both cognitive functions (Kertesz, 1999). Novoa & Ardilia (1987) found that not only did people with left frontal damage show deficits on typically left-lateralized language tasks, those with right frontal damage did as well. Additionally, a comparison of neuroimaging studies of language and executive functioning reveals that there are overlapping areas of activation between these two kinds of tasks (see Binder, 1997, for a review of language areas commonly activated in fMRI, and Fassbender et al., 2004, for an example of an executive study).

The bulk of the evidence available already in the literature comes from empirical studies, which can be grouped into two main types. In the first, people with TBI are tested on executive functioning tasks and language tasks, and researchers look for correlations between scores on the two types of tasks. Hinchliffe et al. (1998) gave extensive batteries of both language and neuropsychological tests to people with TBI and found several significant correlations between factors testing executive functioning and language. Snow et al., (1998) also found that among people with TBI scores on a discourse task correlated with two measures of executive functioning (Trails B and a verbal fluency task). Channon & Watts (2003), again studying persons with TBI, found that a joint score made up of three executive functioning measures accounted for 36% of the variance seen in their discourse task. Similar findings have also been reported in children with TBI (Brookshire et al., 2000; Chapman et al., 2004).

The second type of study showing evidence for influence between executive skills and language is less structured—in this set of studies, errors on language tasks are analyzed, and explanations for people with TBI making errors often revolve around theories of executive control. This type of evidence comes from McDonald and colleagues (McDonald, 1993; McDonald & Pearce, 1995), who found that participants with brain injury had difficulty sequencing information and excluding irrelevant information from their narratives when explaining to a blindfolded person how to play a novel game. Studies reporting errors in making indirect requests (McDonald & van Sommers, 1993), and in problems with inferencing by children with TBI (Dennis & Barnes, 2001) have similarly concluded that executive functioning is contributing to apparent difficulty with language after TBI.

Studies of executive functioning in communicative contexts in the rehabilitation literature are also a source of evidence for questions of the relationship between executive functioning and language. For example, Sohlberg, Sprunk, & Metzelaar (1988) looked at self-monitoring in the context of communication, and reported that gains could be made in verbal initiations and response acknowledgement. Gajar, Schloss, Schloss, & Thompson (1984), however, found that self-monitoring training only increased conversational responses during the time training was going on. Specifically, these studies suggest that rehabilitation in executive functioning could generalize beyond the task used, and lead to lasting results. What they lack, however, is a conclusive way to show that treatment for executive control problems has led to benefits in language processing.

In sum, the evidence about executive functioning and language deficits and differences after TBI reviewed in this section and above suggests that this population is an interesting one with which to examine questions about the interaction between these two cognitive areas. While all the studies discussed in this section are suggestive of a relationship between language and executive functioning, they fall short of elucidating that relationship and offer no advice in the path such investigation should take. In light of this, it may be useful to consider in more detail the features of TBI which could potentially affect executive functioning.

1.4.2 Features of the injury that could be affecting control processes

As discussed above, based on the nature of traumatic brain injury, there are many ways in which executive functions could be affected. Focal lesions may be less common, but when they do occur, they affect the frontal lobes which are clearly important for executive skills. The major impact, however, is delivered by the diffuse axonal injury which can affect the connecting tracts between distributed networks. One potential aspect of control that we have not yet considered, however, is due to hemispheric communication, either cooperation or inhibition. Because this is a site frequently affected by DAI, it deserves some consideration.

1.5 THE CORPUS CALLOSUM

Largely regarded as one of the structures most commonly affected by DAI (see section 1.1.5.1.2), the corpus callosum is an important structure in brain anatomy in that it provides a large portion of the fibers which connect the two hemispheres. Monkey models suggest that connections proceed in topographically organized manner from front to back, with prefrontal at the anterior edge of the corpus callosum (or genu), followed by premotor, sensory, posterior parietal, temporal, and finally occipital connections (Pandya & Seltzer, 1986). This general method of organization seems to hold in the human brain as well (Taber & Hurley, 2007). Connections from an area often reach both that area's own contralateral homologue as well as other contralateral areas.

Corpus callosum issues after TBI have been minimally investigated, but the results of these studies do lead one to conclude that this is an important area of study. One group has called involvement of the corpus callosum the best single predictor of injury severity (Gale et al., 1995). Mathias et al. (2004) found a group of people with TBI to have a smaller callosal volume than matched controls, and an autopsy study reported DAI to be preferentially located in the corpus callosum of road traffic victims (Pittella & Gusmão, 2004). The largest body of evidence on this matter, studies examining DAI with DTI, have found overwhelming evidence of corpus callosum involvement as shown through decreased fractional anisotropy (FA) in the corpus callosum of TBI groups as compared to controls (Inglese et al., 2005; Kraus et al., 2007; Nakayama et al., 2006; Tisserand et al., 2006; though see Bazarian, Zhong, Blyth, Zhu, Kavcic, & Peterson, 2007, for evidence of elevated FA values). Data from our own research group has also shown decreased FA in the corpus callosum, as well as higher diffusivity and a lower number of fibers in that region (Scanlon, Russell, Arenth, & Ricker, 2008). Finally, studies of axons in vitro (e.g., Reeves, Phillips, and Povlishock, 2005), suggest that unmyelinated axons are also vulnerable to DAI and may be more so than myelinated axons. As the corpus callosum contains up to 30% unmyelinated axons (Povlishock, 2008), this may be one additional reason it is likely to be affected. Important for the current study is the fact that a high percentage of the people who have experienced a TBI may have some DAI, which is then likely to have some involvement of the corpus callosum.

1.5.1 Theories of callosal function

While early researchers thought the corpus callosum's role might be purely structural, to help the hemispheres stay up (reported in Lashley, 1929), it seems clear to us now that it has an important role in communication between the hemispheres. What that role is, however, is still relatively unknown. Callosal function research arose largely from work on hemispheric specialization, and from that research many scientists believed that the function of the corpus callosum was to allow these specializations to develop and flourish, though Chiarello (1995) points out that the corpus callosum may not necessarily have only a single function.

Theories of callosal function tend to fall into two camps: those stressing excitation, and those describing an inhibitory role. Note that these generally refer to functional excitation and inhibition, which are not necessarily the same as the neuronal processes of the same names (e.g., excitatory neural signals could be transferred across the corpus callosum but act to inhibit the other hemisphere). There is actually evidence for transfer of both excitatory and inhibitory signals (Bloom & Hynd, 2005; Innocenti, 2009). Theories of excitatory transfer have as evidence the nature of the callosotomy surgery (i.e., that severing the corpus callosum reduces transfer of excitation in the way of seizure activity), and also the finding that people who can complete demanding tasks tend to have a larger callosal area (see Bloom & Hynd, 2005, for a review of these types of evidence).

Inhibitory theories come in several types—one hemisphere could suppress processing in the other, isolate its own processing from the other, or interfere with processing on the other side (Chiarello & Maxfield, 1996). Inhibition could accomplish several different processing outcomes. One theory of inhibitory function (Cook, 1984) has suggested that lateral inhibition of surrounding representations on a single side, combined with homotopic inhibition of the same representation in the homologous area of the other side and subsequent lateral excitation of its surrounding representations, could produce complementary activations across hemispheres. There is evidence from ambiguous word priming that this kind of situation does arise, but no evidence that it is accomplished through the corpus callosum (Chiarello, 1995).

One final theory that should be considered here is that of Banich (1995, 1998, 2003). She posits that, while it might be advantageous to sequester processing to one hemisphere or the other, processing power is increased by using the two hemispheres to process in parallel, and that when faced with complexity, interhemispheric processing will result. This idea is very interesting, and will be discussed in more detail in later sections.

1.6 CONCLUSIONS

Traumatic brain injury affects a large number of people each year, with a preponderance for young males. There can be far-reaching consequences from this type of injury, including physical, cognitive, and psychological among them. Cognitive areas affected include not only memory and executive functioning, but in some situations language as well. The damage to the brain can involve focal lesions, typically occurring in the frontal lobes as well as the temporal poles, but more common is a collection of multifocal microlesions, or diffuse axonal injury. Somewhat misnamed, DAI preferentially affects certain areas, most notably the corpus callosum. Because DAI can be difficult to appreciate on some types of scans, it is likely that the actual percentage of people who have experienced a TBI who have some DAI is quite high. Of those, a large percentage will have corpus callosum involvement because of the frequency with which the corpus callosum is affected by DAI.

The language deficits seen after TBI have been historically difficult to characterize, and some have suggested that they are actually secondary to problems with executive functioning, though evidence for this claim has been minimal. While neuroimaging studies of language after

TBI have not been conducted, those done in other cognitive areas have suggested atypical activation for people with TBI in the right hemisphere. When considered together with the knowledge that many people with TBI have experienced DAI, which can often affect the corpus callosum, these facts lead to the conclusion that it would be useful to include hemispheric factors in an investigation of language and executive functioning after TBI. Designed to begin to address some of these issues, this series of projects has as an aim the investigation of the interplay between language, executive functioning, and hemispheric interaction after traumatic brain injury.

To begin this investigation it was necessary to find well-studied hemispheric language effects that could be thought to have greater and lesser executive demands. Because language at the single word level may be most understudied after TBI as well as because paradigms with hemispheric presentation that do not include eye-tracking must present only a small amount of data at a time, the language literature dealing with presentation of single words was considered. One of the most common paradigms in this literature is priming with lexical decision. Semantic priming has also been widely examined with hemispheric presentation, and it is thought that processing can be manipulated to be automatic or strategic based upon a change in the amount of related stimuli in a block (Chiarello, 1985). Previous data from our lab (see Appendix A) also suggest that persons with TBI do experience semantic priming in a lexical decision task, at least during centrally-presented trials. For these reasons, it was thought that priming with lexical decision and split-hemifield presentation would allow an investigation of whether, in people with TBI, the language processes of the two hemispheres alone are intact and functioning as they do in control subjects, and whether there would be differences in blocks which supported automatic or strategic processing. Thus, the first experiment used split-hemifield presentation of categorically related and unrelated prime-target word pairs to examine whether each hemisphere in people with TBI is processing words like control participants, or whether some low-level language deficit can be found.

While the first experiment dealt with low-level language processing by hemisphere, and had some modest executive manipulations, a second experiment was needed that provided a more robust demonstration of differences based on the level of executive demands. Verb generation is another language task which makes use of the presentation of single words, and the properties of the stimulus items can be made to require greater or lesser executive involvement in the form of selection demands (Thompson-Schill, et al. 1997). This task has also recently been adapted for hemispheric presentation by Chiarello and colleagues (Chiarello, et al., 2006), and was thus thought to be a good candidate for the current investigation. In the second experiment, Chiarello, et al.'s verb generation experiment (2006, Experiment 1) with hemispheric presentation and manipulation of selection demands was replicated to examine the influences of greater executive demand on processing of single words by persons with TBI as compared to controls.

A final important part of the current investigation was to begin to examine the neural basis for any differences found in executive functioning, language, and hemispheric processing between people with TBI and controls. One way of doing this which has recently gained popularity in the literature but has not often been used with the TBI population is using functional connectivity. Therefore, the final experiment is an analysis of fMRI data from another study, which should provide information about the functional connectivity of areas in either hemisphere known to be involved in language and executive functioning.

The knowledge gained from these three experiments should help elucidate the relationships between language, executive functioning, and hemispheric contributions to these in people with TBI as compared to non-injured controls. Based on what we know about the nature of the injury, it is likely that there will be impaired hemispheric communication in the TBI population relative to controls. More impairment will likely be seen as executive demands become greater, with a resulting detriment seen in language performance, and there is expected to be an associated pattern of weaker cross-hemisphere connections in the TBI group.

2.0 EXPERIMENT 1

2.1 INTRODUCTION

Many of the findings about hemispheric representation for language come from three sources: hemsipherically-controlled presentation, split-brain patients, and neuroimaging. Originally, the tendency for the left hemisphere to be dominant for language processing had its roots in neuropsychology by way of Broca and Wernicke, and that tendency was confirmed by unilateral intracarotid sodium amytal injection and unilateral electroconvulsive therapy to hold for fully 96% of right handers and nearly 70% of left handers (Rasmussen & Milner, 1977). Experiments using hemispheric presentation for language stimuli have been done across a variety of modalities—with visual (Goodglass & Barton, 1963), auditory (Bryden, 1963), and even haptic presentations in blind Braille readers (Semenza, Zoppello, Gidiuli, & Borgo, 1996). While left hemisphere advantages are the norm in these kinds of studies, there are some language tasks which consistently elicit right hemisphere advantages—for example, things like prosody comprehension (e.g., Ley & Bryden, 1982), and this right hemisphere advantage for prosody comprehension has also been hypothesized based on studies with people who have right-hemisphere damage (e.g., Weintraub, Mesulam, & Kramer, 1981).

Experiments with people who have experienced a corpus callosotomy (often referred to as a "split-brain" operation) have made it clear that the picture is even more complex. The right hemisphere has some rudimentary language, including being able to read single words. Few patients recover speech from that side, however, and it appears that the right hemisphere uses a whole-word reading strategy, and is unable to perform a grapheme-to-phoneme conversion (Gazzaniga, 2005). For those patients who exhibit evidence of both right- and left-hemisphere lexical knowledge, these also seem to be organized differently (Gazzaniga, 1995).

Finally, experiments employing neuroimaging technology (especially PET and fMRI) have expanded the picture yet further in several ways. First, the extent of language representation in the left hemisphere seems to be much more extensive (or at least more varied) than originally thought (e.g., see Binder, 1997, for a review). Right hemisphere contributions to language processing have also been extended by the inclusion of figurative language and metaphor processing, reasoning, linguistic context usage, cohesion, and repair (see Bookheimer, 2002, for a review). Finally, the cerebellum and other subcortical structures like the basal ganglia and the thalamus would never have been expected to play a role in language processing yet activations in these areas have been found repeatedly by neuroimaging studies (see Fiez & Peterson, 1998 and Cabeza & Nyberg, 2000 for reviews of cerebellar, and general subcortical activity, respectively). However far research in this area has come, though, there is a tendency to focus on specializations of the hemispheres separately, without much consideration of how they work together or interact. Determining more about the interaction between the hemispheres is one of the goals of the current project.

In order to begin this investigation, however, it is necessary to examine whether language processing still proceeds for our TBI group as it does for controls. To this end, a priming study with lexical decision was conducted to investigate whether people with TBI respond to lateralized prime-target pairs in the same manner as do healthy controls. A previous investigation by the author has shown that people with TBI are sensitive to semantic priming (see Appendix A). Pairs of related and unrelated words as well as pairs including nonword foils were presented to the right and left visual fields of participants as they rested in a head-stabilizing apparatus consisting of a chin- and head-rest. Categorically-related pairs (e.g., DEER—PONY) made up the related stimuli because this type of relation has yielded the most clear results in previous studies utilizing only control participants (e.g., Chiarello, Burgess, Richards, & Pollack, 1990). Presentation times for primes and targets were 100 msec each as this duration is thought to be short enough to prevent eye movements from spoiling lateralization effects (Hardyck, Dronkers, Chiarello, & Simpson, 1985). Both prime and target of a pair were lateralized to the same side for similar reasons, while some of the foil trials were presented with prime to one side and target to another. This presentation setup should have discouraged anticipatory eye movements by making it impossible to anticipate where the next word would be presented or program and carry out an eye movement once it appeared.

In the first block of the study, the stimulus set contained a small percentage of related trials, which is thought to lead to automatic lexical access processes. A secondary goal of this experiment was to then test whether strategic lexical access is also normal in each hemisphere. To do this a second block of trials was included with a high percentage of related trials, which is thought to lead to controlled processing (Neely, 1977; see Schneider & Schiffrin, 1977, for a discussion of automatic and controlled processing). While priming studies can lead to different results based on the slightest parameter change, the research the current experiment is based on (Chiarello et al., 1990; Chiarello & Richards, 1992; Chiarello, Richards, & Pollack, 1992) has found priming in both hemispheres when there is a high percentage of related trials, and priming in the right hemisphere only when there is a low percentage of related trials.

In the current experiment, priming effects in the two blocks were assessed for both controls and people with TBI. The data from the controls were expected to replicate that found in previous work. If the TBI group showed atypical effects of lateralization in the automatic condition then impaired language processes in one hemisphere or another are likely to blame. If, however, performance on automatic semantic priming showed the normal pattern but differences were found in the controlled access condition, it is likely that controlled lexical access is contributing to the problem. Whether this is a larger issue of executive control is a question which will be addressed further by Experiment 2. If no between-group differences were found in Experiment 1, but there are differences in Experiment 2, then hemispheric differences may be due to higher-level control processes and not to language processing specifically. As discussed above, it is this latter possibility that seems the most likely.

As a further test of whether executive issues affect language processing in our TBI population, some bilaterally presented trials were also included. In studies like the current one, healthy controls typically show a benefit of greater accuracy and in some cases also faster response times for trials which are presented bilaterally (e.g., Hasbrooke & Chiarello, 1998; Mohr, Endrass, Hauk, & Pulvermüller, 2007; Mohr, Pulvermüller, Cohen, & Rockstroh, 2000). This effect is known as the bilateral redundancy gain, and it has been suggested that this pattern shows evidence of cooperation between the hemispheres (Mohr et al., 2000). Some patient populations which are known to have disturbances in white matter tracts, like in schizophrenia, have been tested on similar paradigms, and contrary to controls they do not show this bilateral redundancy gain (Mohr et al., 2000), a finding which is perhaps evidence of disordered communication between the hemispheres. As discussed above, TBI can also lead to problems with the connections in the brain, especially between the two hemispheres, and so it was hypothesized that including bilaterally-presented trials might show an absence of the bilateral redundancy gain in the TBI population as well.

2.2 METHOD

2.2.1 Participants

Participating in the first two studies presented here were 19 persons who have experienced a TBI (3 females, 16 males) and 19 healthy controls (3 females, 16 males). All participants were between the ages of 18 and 55, had normal or corrected-to-normal vision, were right handed, and were native speakers of English. The people with TBI were 1-3 years post-injury to ensure sampling of people in the chronic phase (Yamaki, Yoshino, Fujimoto, Ohmori, Imahori, & Ueda, 1996), and they had a definitive diagnosis of TBI as defined by the TBI Model Systems National Database (Harrison-Felix et al., 1996; see section 1.1.1). Because of the variability in mild TBI, included in the current study were only people who sustained either a moderate, severe, or complicated mild injury. Moderate and severe injuries are defined as the lowest Glasgow Coma Score (GCS, Teasdale & Jennet, 1974) in the first 24 hours after injury being less than 13. Complicated mild injuries are mild injuries ($GCS > 13$) with accompanying neurological or radiological findings (Williams, Levin, & Eisenberg, 1990). These kinds of complicated mild injuries have been shown to cause behavioral performance like that found with moderate or severe injury (e.g., Kashluba, Hanks, Casey, & Millis, 2008). Thus although the TBI group may seem diverse, the actual behavioral performances of the participants were expected to be in the same range.

Actual initial GCS scores of the included participants ranged from 3 to 14, with a mean of 4.63 (SD = 3.88), and a median score of 3. Because many initial GCS scores are reflective of the fact that patients are often assisted in breathing and given paralytic medication, the best GCS score in the first 24 hours was also recorded wherever possible. The mean best GCS score in the first 24 hours after injury was 9.44 (SD = 3.11), with a median score of 9. Based on initial GCS score, 16 participants would be classified as having sustained a severe injury, 2 were moderate, and 1 was complicated mild. Based on best GCS in 24 hours, 9 persons had a GCS in the severe range, 6 in the moderate range, and 3 in the complicated mild range. Either metric suggests that the sample included in this study was relatively severely affected. Time since injury for these participants ranged from 0.99 years to 3.06 years, with a mean of 1.87 years (SD = 0.73), and a median value of 1.81 years. At least 70% of the people with TBI had returned to work or school at the time of testing.

Healthy controls were matched to people with TBI based on age, years of education, and gender. It was attempted to find paired matches within one year of education and within five years of age. Most matches were closer than that, with very few matched pairs falling outside that target. Age and education levels were not significantly different between groups (Age: t(18) = 0.28, p = 0.78; education: t(18) = -0.08, p = 0.94). People in the TBI group ranged in age from 19 to 55, with a median age of 36 and a mean age of 35.63 (SD = 11.81). Controls ranged in age from 20 to 52, also with a median age of 36 and with a mean age of 34.68 (SD = 11.59). Education ranges were 12-18 (TBI group) and 10-17 (Controls), with median scores of 13 and 14, respectively (TBI M = 13.68, SD = 1.83; Control M = 13.74, SD = 2.13). Full participant demographics can be seen in Table 2.1. All participants were found to be right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). One additional control participant completed the study but is not included in any count or analysis as he was classified as ambidextrous on the Edinburgh Handedness Inventory and was thus excluded. All other participants in both groups were clearly right hand dominant on this scale (Controls: M = 93, SD = 14; TBI group: M = 90, SD = 11).

Table 2.1. Participant Demographic Information, Experiments 1 and 2

Subject	Sex	Age (C)	Education (C)	Initial GCS	Best GCS in 24 hrs	Time post-injury (yrs)	Etiology	TBI Type
201	M	55 (52)	16 (14)	3 TP	7	1.51	MCA	SAH & IPH
202	M	40 (42)	13 (16)	3 TP	8 T	2.90	Fall	IPH & SAH
203	M	55 (51)	13 (12)	14	15	1.47	MVA	SDH, SAH, HC
204	F	31 (28)	13 (16)	3 TP	12 T	2.93	MVA	DAI
205	M	47 (46)	16 (16)	3 TP	11	2.90	MCA	SDH, EDH, SAH
206	M	22 (20)	14 (14)	3 TP	6 T	1.81	MCA	SDH, SAH
207	M	36 (36)	13 (10)	3 TP	6 T	1.08	MVA	DAI
208	M	48 (52)	12 (12)	3 TP	7	2.78	MVA	SAH
209	M	29 (25)	16 (16)	13	13	1.63	MCA	SAH, SDH
210	M	33 (33)	12 (12)	3 TP	6 TP	2.06	MCA	DAI, EDH
211	F	40 (36)	12 (11)	3 TP	11	2.12	MCA	DAI, SAH
212	M	25 (25)	18 (17)	3 TP	11 T	1.03	Fall	SDH, SAH
213	F	24 (24)	16 (16)	13	15	3.06	MVA	SDH, SAH
214	M	41 (41)	14 (13)	3 TP	8 TP	1.04	MCA	SDH
215	M	19 (21)	12 (12)	3 TP	8	1.87	MVA	ICH, DAI?
216	M	19 (20)	13 (14)	3 TP	11	1.07	MVA	DAI
217	M	51 (47)	12 (12)	3 TP	10 TP	1.36	MVA	EDH
218	M	25 (21)	13 (16)	3 TP	unknown	0.99	MVA	DAI, SAH, SDH
219	M	37 (39)	12 (12)	3 TP	5 T	2.01	MVA	HC, SAH

The age and education values for each subject's paired control are given in parentheses. All pairs were of the same gender.
Abbreviations: GCS = Glasgow Coma Score, T = intubated, P = given paralytic medication, MCA = motorcycle accident, MVA = motor vehicle accident, SAH = subarachnoid hemorrhage, IPH = intraparenchymal hemorrhage, SDH = subdural hemorrhage, HC = hemorrhagic contusion, EDH = epidural hemorrhage, ICH = intracerebral hemorrhage, DAI = diffuse axonal injury

Study procedures were approved by the University of Pittsburgh's Institutional Review Board (IRB). Participants were recruited with IRB-approved fliers as well as through referrals and the Department of Physical Medicine and Rehabilitation Research Registry (people with TBI only). All participants signed informed consent, and were compensated $25 for their participation in these two experiments.

2.2.2 Materials and Design

Materials included pairs of words that were categorically related as described in section 2.1, unrelated pairs, and nonword pairs for each block. Each block consisted of 80 word trials and 80 nonword trials, for a total of 320 trials in the experiment. Two blocks were included that varied the ratio of related and unrelated pairs, in an attempt to encourage more and less strategic processing of the words, as discussed in the introduction to this chapter. The word trials in the first block were 25% related (10 experimental trials each on the right and left) and 75% unrelated (10 experimental trials each on the right and left, as well as an additional 20 unrelated filler trials each on the right and left). The second block had the percentages and numbers of trials reversed to make 75% related and 25% unrelated.

Presentation of the word pairs was controlled such that experimental trials appeared with both prime and target being presented in the same visual field, one after the other. Filler pairs and nonword pairs appeared with the first word on one side and the second word on the other side more than half the time, such that the overall experience of the participant was that they could not predict on which side the second word would appear. This kind of presentation was important to discourage participants from holding their eyes somewhere besides the center of the display. For the final 13 people in each group, 12 word filler trials in each block were presented with the second word appearing simultaneously in both hemispheres, i.e., bilaterally. This change in presentation for a small number of trials allowed the additional hypothesis about bilateral redundancy gain to be explored.

Stimuli were taken from a number of experiments using priming paradigms as these types of experiments are common in the literature and using previous stimuli increases the chances of successful replication of effects. All related experimental word pairs were taken from a previous study by Chiarello et al., (1992). Unrelated experimental trials were also from Chiarello et al., (1992), with additional pairs from Brown et al. (2006), to generate a sufficient number of pairs. Related filler pairs were taken from Chiarello et al. (1990). Unrelated filler pairs as well as nonword trials were taken from Brown et al. (2006). Because of collection of stimuli from different sources, calculations were done to ensure that groups of stimuli were properly matched. Unrelated and related experimental trials were found not to differ on familiarity, imageability, frequency, or length calculated in three ways (number of letters, number of phonemes, and number of syllables). Whether a target word (the second of the pair) appeared in the right or left hemisphere was counterbalanced by subject, such that half of the participants saw a word on the right, and half on the left. The two groups of words appearing in one hemisphere or the other were equivalent on all the dimensions given above for the related vs. unrelated comparisons. Finally, the words and nonwords were compared for length as defined in number of letters, and also found not to be significantly different. Statistics for these comparisons are listed in Table 2.2, and all stimulus items are given in Appendix B.

Table 2.2. Descriptive Statistics for Items from Experiment 1

Measure	Left in List A, M (SD)	Right in List A, M (SD)	t-test
Familiarity*	540.22 (54. 75)	545.92 (49.84)	t(157) = 0.688, p = 0.493
Imageability	572.92 (49.44)	578.79 (44.24)	t(157) = 0.788, p = 0.43
Frequency	62.69 (89.10)	79.34 (130.70)	t(150)= 0.922, p = 0.358
Length (# letters)	4.45 (0.90)	4.36 (0.83)	t(158) = -0.640, p = 0.523
Length (# phonemes)	3.60 (0.92)	3.45 (0.94)	t(158) = -1.019, p = 0.310
Length (# syllables)	1.29 (0.48)	1.19 (0.39)	t(158) = -1.438, p = 0.152

Measure	Related Trials, M (SD)	Unrelated Trials, M (SD)	t-test
Familiarity	540.05 (52.80)	546.09 (51.85)	t(157) = -0.727, p = 0.468
Imageability	581.47 (42.98)	570.25 (50.02)	t(157) = 1.502, p = 0.135
Frequency	65.25 (105.23)	75.92 (116.96)	t(150) = -0.590, p = 0.556
Length (# letters)	4.38 (0.88)	4.44 (0.86)	t(158) = -0.457, p = 0.649
Length (# phonemes)	3.53 (1.06)	3.53 (0.80)	t(158) = 0.000, p = 1.000
Length (# syllables)	1.30 (0.46)	1.18 (0.41)	t(158) = 1.804, p = 0.073

Measure	Word, M (SD)	Nonword, M (SD)	t-test
Length (# letters)	4.54 (0.85)	4.61 (0.76)	t(637) = -1.061, p = 0.289

* Familiarity, imageability, and frequency counts were obtained from the MRC Psycholinguistic Database: Machine Usable Dictionary Version 2.00 (http://www.psy.uwa.edu.au/mrcdatabase/mrc2.html). Familiarity and imageability are based upon three merged sets of norms (see Appendix 2 of the MRC Psycholinguistic Database User Manual (Coltheart, 1981) for more details), and range from 100-700. Frequency is based on the Kucera and Francis written frequencies (Kucera & Francis, 1967).

The experiment was programmed using E-prime presentation software (www.pstnet.com). All 320 trials were presented in one session, with short breaks permitted at the halfway point of each block, and a longer break between blocks. A response box was used to collect manual responses, and all participants used their right hands to respond. Each trial began with a fixation period made up of 350 msec of a black fixation cross in the screen's center, followed by 50 msec of a red fixation cross in the same location, which was followed by a black fixation cross for another 50 msec. This design is thought to encourage fixation at the central point by making the fixation cross appear to "blink" from black to red and back to black. The prime word was then presented for 100 msec, followed by another fixation screen for 300 msec and then a 100 msec target word. Following the target word, a subject-terminated probe screen containing a question mark above the fixation cross appeared. There was an additional 1000-msec blank screen to make the experimental pacing more acceptable for the TBI population without compromising the timing of the prime and target. The timing of these two elements is important because if they were presented for a longer period of time, it might be possible for the participant to move his or her eyes to the word, which would compromise the single-hemifield presentation. The trial design is presented graphically in Figure 2.1.

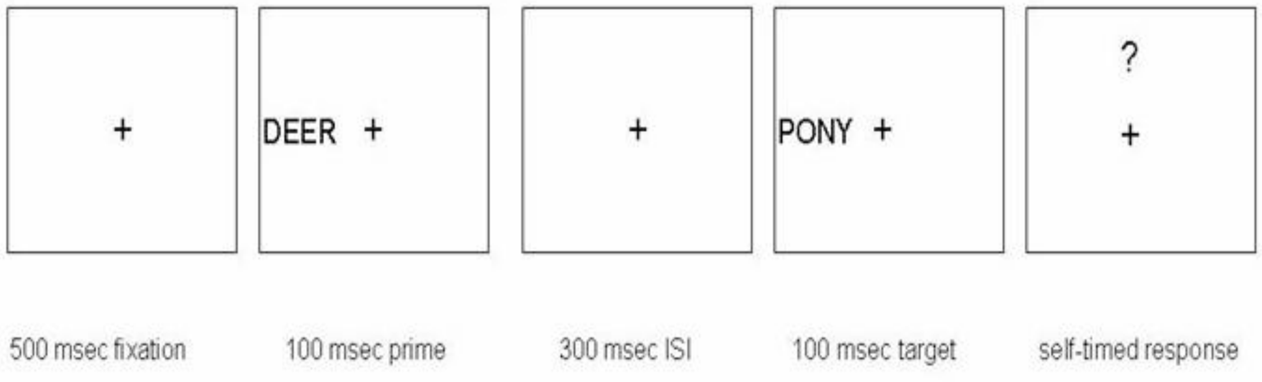

Figure 2.1. Trial Design, Experiment 1

2.2.3 Procedure

Following informed consent, participants were seated at a computer with a head restraint device (chin rest with forehead bar) in front of it. The participants were seated with their eyes approximately 60 cm from the computer screen (as in the works cited throughout this section). Participants were first given practice with the task and were informed of the importance of keeping their eyes at the fixation point at all times. They were told that they would see two words, one after the other, and they should ignore the first word and make a response (word/non-word) to the second. The low-related and high-related blocks were run in the same order for each person (low, then high) to prevent participants from expecting a high percentage of related items in the low-related block. All subjects also participated in the second experiment. After the computer tasks, the Edinburgh Handedness Inventory (Oldfield, 1971), with an expansion to collect information on handedness of family members, was completed.

2.3 RESULTS

Repeated measures analyses of variance (ANOVAs) as well as planned contrasts were performed on the response times and accuracy values collected in this experiment (see Table 2.3)[1]. These measures provided data on a number of factors including priming effects, automatic and controlled

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[1] Note that there are other statistical alternatives for analysis of these data, including multiple regression or the sole use of planned comparisons (Miller, 2007; Rosenthal & Rosnow, 1985). As the latter would have missed potentially interesting interactions and the former has been described as especially relevant for continuous or correlated independent variables, the ANOVA method was chosen despite its possibly inefficient nature.

processing, attentional factors, bilateral redundancy gain, and visual field effects as well as group differences related to these. Each of these factors will now be discussed in turn.

Table 2.3. Descriptive Statistics, Experiment 1

Group	Condition, Visual Field	RT M (SD), msec	Accuracy M (SD), %
Control	Related, right	683.41 (146.64)	85.26 (12.41)
	Related, left	731.95 (176.76)	82.63 (12.06)
	Unrelated, right	687.74 (150.19)	84.74 (10.86)
	Unrelated, left	698.50 (127.31)	82.63 (13.68)
TBI	Related, right	898.39 (244.57)	77.89 (18.81)
	Related, left	924.01 (226.80)	78.16 (18.72)
	Unrelated, right	888.71 (251.14)	83.95 (11.97)
	Unrelated, left	918.24 (218.15)	79.47 (14.99)

2.3.1 Automatic vs. controlled processing

The two blocks of this experiment contained different numbers of related trials in an attempt to manipulate the type of processing being done by participants. Block 1 contained a small percentage (25%) of related trials in an effort to induce more automatic processing, while Block 2 contained 75% related trials to encourage controlled processing. Unfortunately, the blocks had to be run in that order for all subjects to experience both types of processing. Repeated measures ANOVAs comparing the factors of Block (1,2) and Group (Control, TBI) suggest that the practice trials may not have been numerous enough to overcome practice effects, as Block 2 was generally found to be faster (subjects: $F(1,36) = 18.82$, $p < 0.001$; items: $F(1, 318) = 66.474$, $p < 0.001$) though not more accurate (subjects: $F(1,36) = 2.87$, $p = 0.099$; items: $F(1,318) = 0.876$, $p = 0.350$). The main effect of group, with a benefit for controls, was also significant in most of these analyses (accuracy, subjects: F(1,36) = 1.742, p = 0.195; accuracy, items: F(1,318) = 17.282, p < 0.001; RT, subjects: F(1,36) = 10.820, p = 0.002; RT, items: F(1,318) = 551.296, p < 0.001). The only significant interaction was for RT in the items analysis (F(1,318) = 15.143, p < 0.001), and suggested that the TBI group improved more from Block 1 to Block 2 than did the control group. All other interactions were non-significant.

Overall, these results suggest that there was improvement from Block 1 to Block 2, perhaps more so for the TBI group (see Figure 2.2). Because the processing types were segregated by block, and the blocks were run in the same order for all participants, it cannot be determined whether this finding results from the effect of increased practice from Block 1 to Block 2, or whether it is due to the mode of processing difference. Because of this difficulty, block has been left out of all subsequent analyses as a factor.

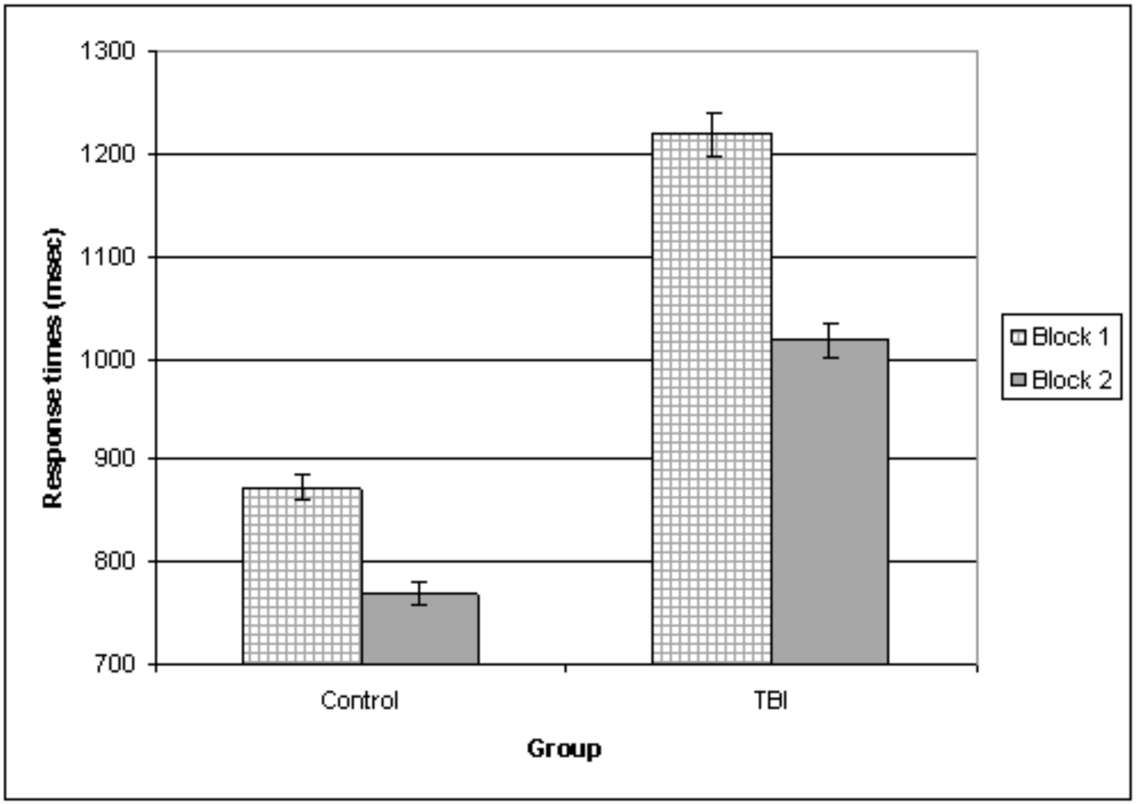

Figure 2.2 Response times were significantly faster in Block 2 for both groups.

2.3.2 Omnibus ANOVAs

Following from section 2.3.1, above, omnibus ANOVAs were conducted on the RT and accuracy data collapsed across blocks with the following factors included: visual field (left, right), relatedness (related, unrelated), and group (control, TBI). In the subjects analyses for accuracy, there were no significant main effects or interactions (all ps > 0.16). The accuracy analysis by items revealed a significant main effect of group (F(1, 78) = 9.212, p = 0.003) such that controls were found to answer more accurately. There was also a marginal main effect of visual field such that trials presented in the right visual field were generally processed more accurately (F(1,78) = 3.347, p = 0.071).

Group effects of the same direction (i.e., with controls showing better performance) were also evidenced in the RT record in both subjects and items analyses (subjects: F(1,36) = 13.394, p = 0.001; items: F(1,78) = 134.208, p < 0.001). No other significant main effects or interactions were found by these analyses (all ps > 0.22).

2.3.3 Priming Effects

One-tailed t-tests were done to look for priming effects (i.e., related words being processed faster or better than unrelated words). These were done separately by group and visual field. The only comparison that reached significance was for the TBI group in the right visual field for accuracy (t(18) = -1.786, p = 0.046), though it was in the wrong direction—with unrelated pairs being answered more accurately than related pairs. All other ps were greater than 0.1 (see Table 2.4). These results suggest either a) no priming took place in this study or b) there were power issues obscuring any potential priming results. As many priming studies include more participants, and the

TBI group in some cases showed a reversal of typical priming effects, the latter of these cannot be ruled out.

Table 2.4. Planned Contrasts for Priming Effects by Group and Visual Field

Group	Condition	Unrelated -Related	t-tests (one-tailed)
Control	RVF (RT)	3.55 msec	t(18) = -0.292, p = 0.387
	LVF (RT)	-33.45 msec	t(18) = 1.280, p = 0.109
	RVF (Accuracy)	-.52%	t(18) = 0.195, p = 0.424
	LVF (Accuracy)	0%	t(18) = 0 .000, p = 0.50
TBI	RVF (RT)	-9.68 msec	t(18) = 0.384, p = 0.353
	LVF (RT)	-5.77 msec	t(18) = 0.138, p = 0.446
	RVF (Accuracy)	6.1%	t(18) = -1.786, p = 0.046
	LVF (Accuracy)	1.3%	t(18) = -0.478, p = 0.319

2.3.4 Attentional Factors

While all participants are asked to keep their eyes focused on the central fixation cross, it is known that the link between where the eyes are and where attention is focused is not perfect—we can, for instance, be attentive to something happening behind us without turning around. Because of this, even when the participant is complying with the instructions, they will likely take longer to respond to trials where attention must be shifted from one visual field to the other (“shift” trials) than trials where the two words are presented one after another in the same visual field (“same” trials). 2 X 2 ANOVAs comparing trial type (same, switch) and group were computed on both response time and accuracy data.

Response times were significantly faster for same trials than switch trials in both the analysis by subjects (F(1, 36) = 33.43, p < 0.001) and by items (F(1, 318) = 29.25, p < 0.001). See

Figure 2.3. for a graphical representation of these results. There was not a significant interaction found between trial type and group in either analysis (subjects: F(1, 36) = 0.48, p = 0.49; items: F(1, 318) = 0.002, p = 0.963). There was a main effect of group in both of these analyses as well, such that controls responded faster overall (subjects: F(1, 36) = 9.81, p = 0.003; items: F(1,318) = 475.98, p < 0.001).

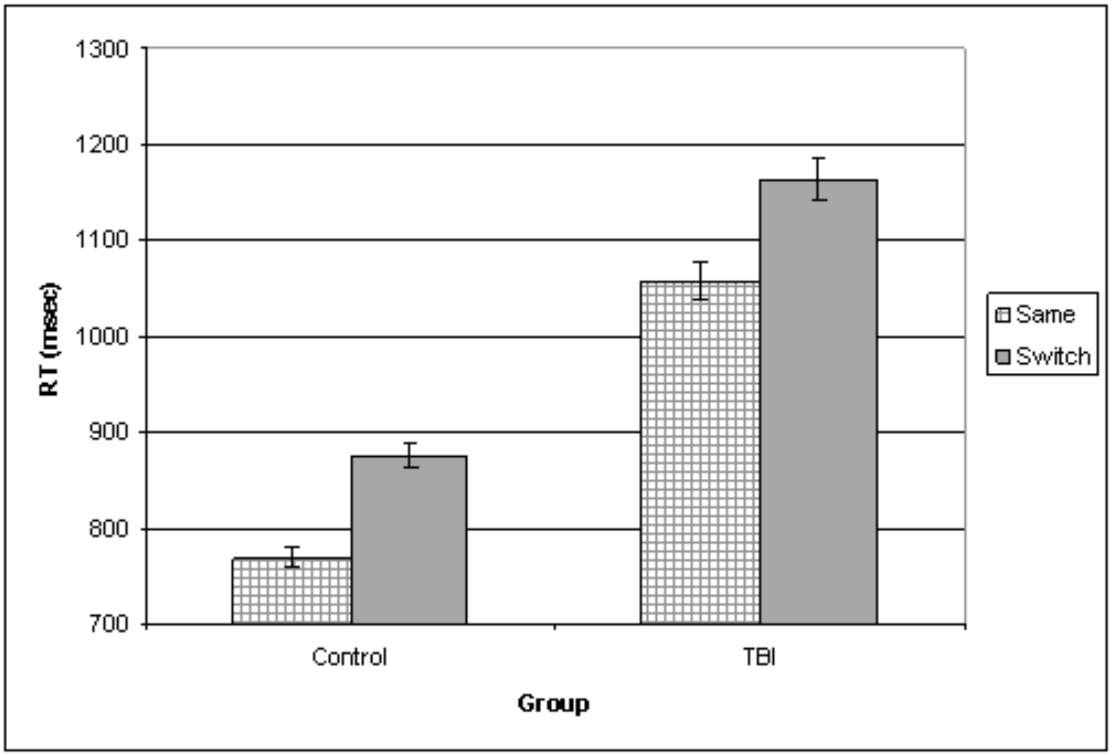

Figure 2.3. Same trials are faster than switch trials.

The results from the accuracy record showed some similarities as well as some differences. A similar benefit for same trials over switch trials was found for accuracy, with main effects of trial type in both analyses (subjects: F(1, 36) = 100.70, p < 0.001; items: F(1, 318) = 146.84, p < 0.001). There was, however, a significant interaction that was evidenced in both analyses (subjects: F(1, 36) = 4.71, p = 0.04; items: F(1, 318) = 15.98, p < 0.001). The nature of this interaction was such that both groups performed similarly on switch trials but controls performed more accurately on same trials than the TBI group. That difference on same trials drove the main effect of group, with controls tending to respond more accurately, that was present in the items analysis (F(1, 318) = 15.60, $p < 0.001$, but not in the subjects analysis (F(1, 36) = 1.45, p = 0.24). These results are displayed in Figure 2.4.

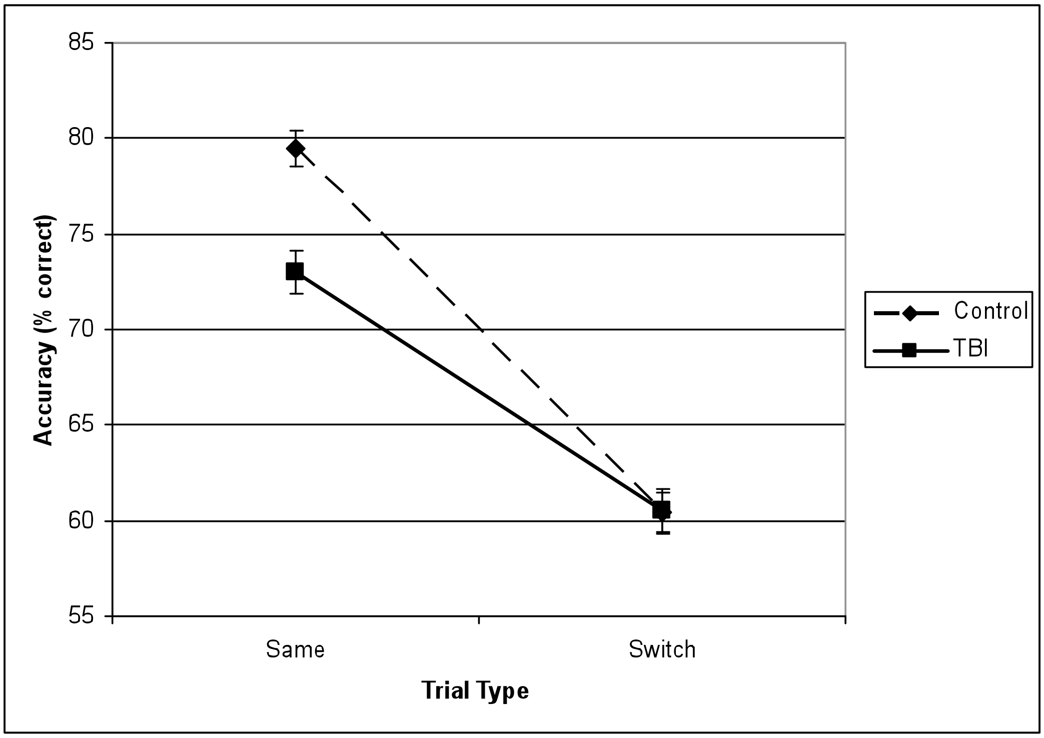

Figure 2.4. The control group shows a greater benefit of same over switch trials.

Overall, the results described in this section seem to suggest that both groups are compromised by having to shift attention during switch trials. This reduction is evidenced both in slower reaction times as well as decreased accuracy and is consistent with prior literature. Controls seem to be performing generally better overall, but their accuracy during switch trials is not different from the TBI group score. This finding may be indicative of impaired processes of attentional switching in the TBI group—they are equally hurt by switch trials, but they fail to show as large a benefit from same trials as controls.

2.3.5 Bilateral Redundancy Gain

As described above, bilateral redundancy gain is an effect showing that presenting the same word bilaterally instead of in only one visual field is associated with response benefits in unimpaired populations. A lack of this benefit is shown in people with schizophrenia (Mohr et al. 2000) which is another condition known to affect white matter. Repeated measures ANOVAs and planned comparisons were computed on the data from the current study to compare unilaterally- and bilaterally-presented trials by group.

Response time analyses revealed no main effect of trial type in either analysis (subjects: F(1, 24) = 1.51, p = 0.23; items: F(1,182) = 1.63, p = 0.20). There was an interaction that reached significance in the items analysis only (subjects: F(1, 24) = 0.12, p = 0.73; items: F(1,182) = 4.89, p = 0.03). This interaction can be seen in Figure 2.5, and is such that the TBI group is slower during bilateral trials than unilateral trials (t(182) = -1.82 p = 0.04) while controls do not show a difference between trial types (t(182) = 0.23p = 0.41). Finally, there was also a main effect of group in both the subjects and items analyses such that controls responded faster overall (subjects: F(1, 24) = 9.57, p = 0.0005; items: F(1, 182) = 194.30, p < 0.001).

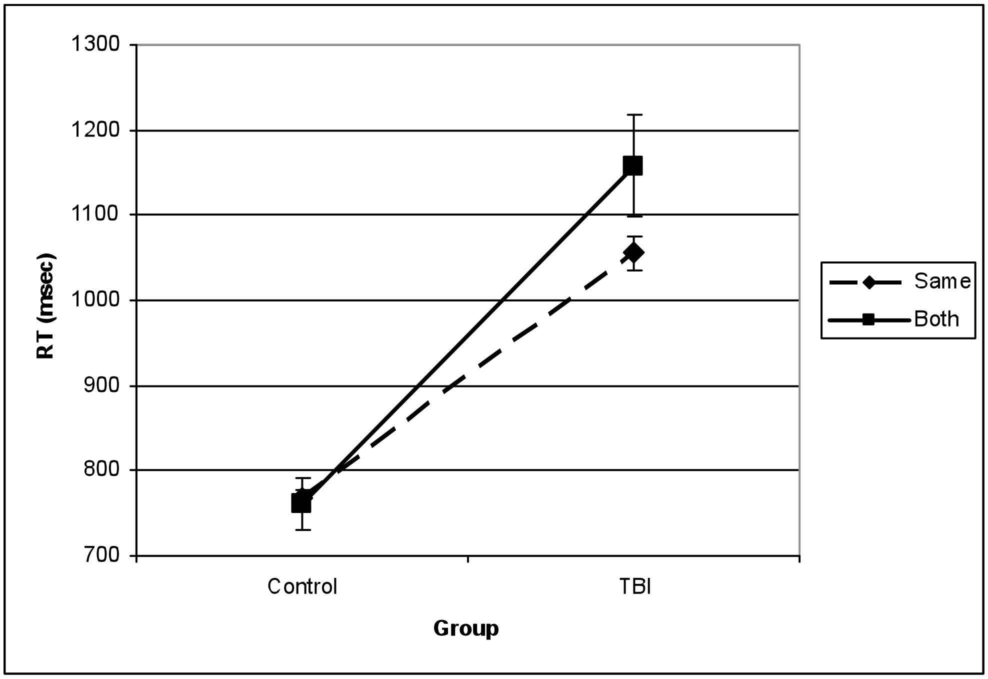

Figure 2.5. TBI group participants are slower to respond to bilaterally presented trials.

Accuracy analyses, on the other hand, did uncover a main effect of trial type such that bilateral trials were responded to more accurately than unilateral trials (subjects: F(1, 24) = 23.79, < 0.001; items: F(1, 182) = 24.20, p < 0.001). No significant interaction was found in either analysis (subjects: F(1, 24) = 0.47, p = 0.50; items: F(1,182) = 2.16, p = 0.14). A significant group effect such that controls were more accurate overall was found in the items analysis only (subjects: F(1, 24) = 1.62, p = 0.22; items: F(1,182) = 11.18, p = 0.001).

Many interesting findings have emerged in this section. First, the controls did not show a benefit in response time for bilateral trials as has been found previously and discussed above. This finding may be due to the large age and education range included in this study, as reaction time benefits were not found in the other study cited above using a non-undergraduate population (Mohr et al., 2000). As in previous works, both groups did, however, show a benefit in accuracy for this type of trials. Most importantly, the people in the TBI group did exhibit response time slowing for bilateral trials as compared to unilateral trials.

2.3.6 Influence of Visual Field of Presentation

Visual field by group ANOVAs were computed for both dependent variables, using only trials where both words were presented on the same side. Again the control group performed faster (subjects: F(1,36) = 4.697, $p = 0.037$; items: F(1, 159) = 418.082, $p < 0.001$) and more accurately (subjects: F(1,36) = 10.940, $p = 0.002$; items: F(1, 159) = 45.424, $p < 0.001$). Visual field differences were revealed in the accuracy analysis, but not in the reaction time analysis, such that trials presented in the right visual field were responded to more accurately (subjects: F(1, 36) = 3.314, $p = 0.077$; items: F(1,159) = 6.866, $p = 0.010$). Refer to Figure 2.6. No significant interactions were seen between the factors of group and visual field.

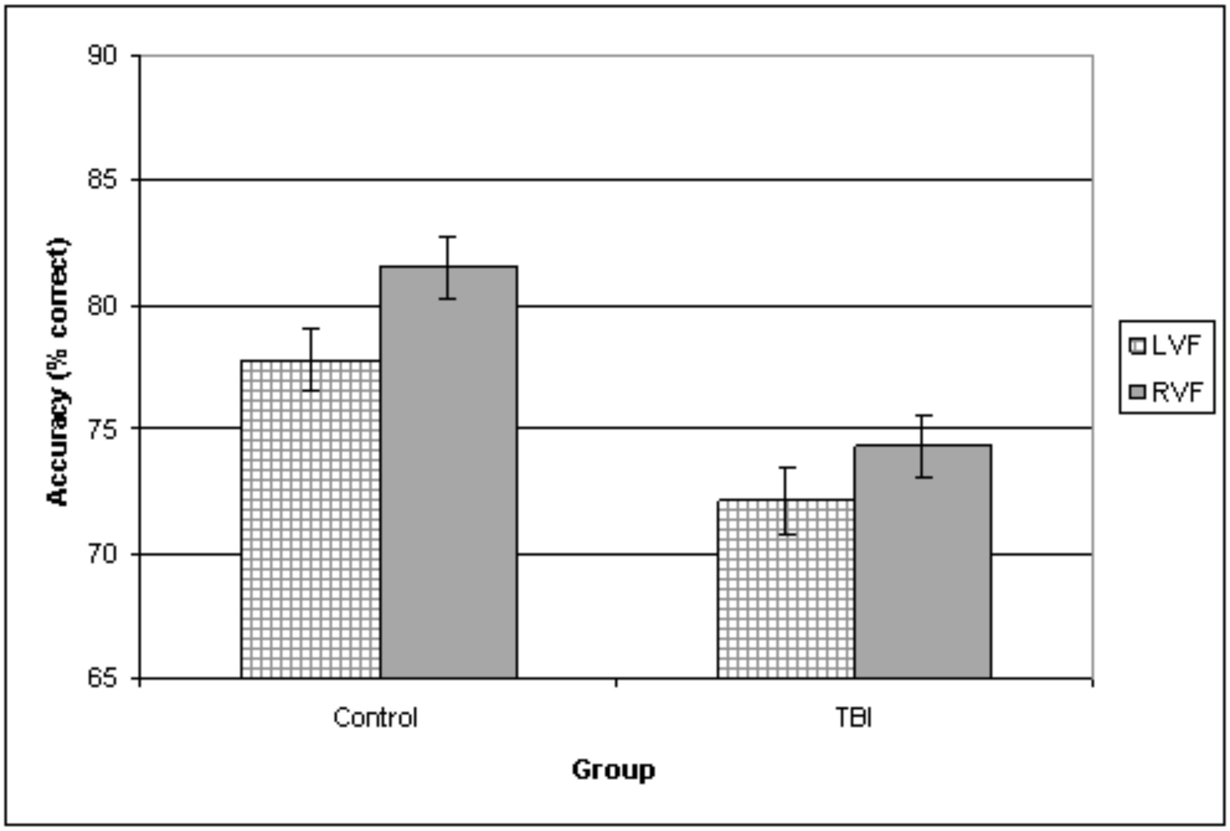

Figure 2.6. Responses to words presented in the right visual field are more accurate.

Planned comparisons were done to look for visual field advantages separately by group and stimulus type (related or unrelated). Although all were in the predicted direction, none of these reached significance though the comparison for the TBI group for accuracy of unrelated pairs came close (p = 0.079; see Table 2.5 for all comparisons).

Table 2.5. Planned Contrasts for Right Visual Field Effects by Group and Trial Type

Group	Condition	Left - Right	t-tests (one-tailed)
Control	Related (RT)	48.54 msec	t(18) = 1.375, p = 0.093
	Unrelated (RT)	10.76 msec	t(18) = 0.562, p = 0.291
	Related (Accuracy)	-2.6%	t(18) = -1.157, p = 0.131
	Unrelated (Accuracy)	-2.1%	t(18) = -0.657, p = 0.260
TBI	Related (RT)	25.62 msec	t(18) = 0.519, p =0.305
	Unrelated (RT)	29.53 msec	t(18) = 0.733, p = 0.237
	Related (Accuracy)	-2.7%	t(18) = 0.049, p = 0.481
	Unrelated (Accuracy)	-4.5%	t(18) = -1.475, p = 0

2.3.7 Correlations with Participant Variables

In order to see whether any of our demographic variables might be predictive of performance on this task, overall RT and overall accuracy scores as well as a measure of visual field preference and a measure of priming for each participant were entered into correlational analyses with the following demographic variables: age (both groups), education (both groups), time since injury, initial GCS score, best GCS score in 24 hours, and handedness score (both groups). The visual field preference measure was obtained by subtracting each subject's RVF RT from his or her LVF RT. The priming score was similarly calculated using the RT for related and unrelated experimental trials.

Most of these correlations did not reach significance. Of those that did, some would have been expected based on previous work. For example, RT was positively correlated with age (r (38) = 0.338, p = 0.038) and accuracy was positively correlated with education level (r(38) = 0.371, p = 0.022). Education was also correlated with priming (r (38) = -0.329, p = 0.043), as was handedness score (r(38) = 0.563, p = 0.012).

As far as injury variables are concerned, initial GCS was not correlated with any other measure. This lack of findings is reasonable in that many people come into the emergency room sedated and intubated, and thus will receive a GCS of 3 regardless of actual injury severity. However, best GCS in 24 hours was positively correlated with accuracy ($r(38) = 0.520$, $p = 0.027$), and the negative correlation between time since injury and visual field preference neared significance ($r(38) = -0.418$, $p = 0.075$). The latter of these, should it turn out to be significant in future studies, would suggest interesting things about the nature of reliance on hemispheric specialization during the recovery process. For example, it may be the case that having stimuli presented directly to the hemisphere which is better able to process it helps to focus processing soon after injury but that this benefit becomes less important later in the recovery process. Other possible explanations would rely on right hemifield attentional bias seen after TBI (e.g., Pavlovskaya, Groswasser, Keren, Mordvinov, & Hochstein, 2007), or a hypothesis of asymmetric hemispheric recruitment such that recruiting the opposite hemisphere is easier starting in the left hemisphere than the right. All of these remain speculations to be tested in future work, however.

2.4 DISCUSSION

While some interesting findings have arisen from this study, overall it appears that some contrasts may have been suffering from a lack of power, most notably the one between related and unrelated trials. The absolute number of each type of trial per block was compromised in an effort to manipulate the percentage of related and unrelated trials in each block. Unfortunately, this may have led to the distinct lack of priming effects seen here. Planned comparisons revealed that the only situation under which priming was appreciated was for words presented in the RVF of people in the TBI group. Possible reasons for this will be considered in the discussion of group differences below. Another methodological challenge for this study was the fact that in order to keep the manipulation of processing type valid across blocks, the low percent related block always had to be first, which made it impossible to rule out a potential practice effect when directly comparing data from the two blocks. The fact that Block 2 was found to be significantly faster would support this idea. The manipulation of visual field, while showing a benefit in accuracy for the RVF, generally returned nonsignificant results. It is likely that this manipulation also suffered from a lack of power, but the accuracy result is suggestive that an experiment with greater power would find a more robust visual field effect in the expected direction.

While the controlled vs. automatic processing distinction was not able to be examined by this study, there were two additional manipulations which got at the question of whether language situations with more control demands would be more difficult for the TBI group—first a comparison was made between trials where attention had to be kept the same, and trials where attention had to be switched from one side to the other. As would be expected from years of previous study on attention, both groups were slower to respond to “switch” trials. Non-switch trials were also found to be more accurate, and there was an interaction between this factor and the factor of group, such that both groups were hurt equally by switch trials, but the controls showed a better recovery with trials where attention remained on the same side.

The other executive manipulation included here was the addition of some bilaterally presented trials. These have shown a benefit in accuracy (and sometimes RT) for control subjects, but not for participants with schizophrenia (Mohr et al., 2000). There was an overall finding that the bilateral trials were more accurate, and this held separately for each group. As far as RT was concerned, however, there was an interaction between group and trial type such that, while the controls showed equal response times for both trial types, the TBI group displayed response times that were much slower for bilaterally presented trials, suggesting that this group needed extra time to deal with these trials, even if they did ultimately end up being more accurate.

Finally, it is the group effects that this experiment was really designed to unearth. Fairly consistent group differences were found throughout this experiment such that the control group was responding faster and also generally more accurately than the TBI group. The latter group showed more sensitivity to priming in the RVF, and exhibited differences in the attentional analysis and for bilaterally presented trials. These results are consistent with the TBI literature, but the patterns of responding were, on the whole, not different from controls in terms of how they responded to different types of trials on the language manipulation. The findings taken as a whole suggest that speed of processing and executive factors may be more of a factor than language processing per se. While this experiment had some methodological issues, there were some data gained that supported the idea that the TBI group had disproportionate difficulty during language processing with higher executive demands. The next experiment is designed to look at language under load in yet another way.

3.0 EXPERIMENT 2

3.1 INTRODUCTION

Verbal fluency is one area in which persons with TBI are reported to have difficulty (Catroppa & Anderson, 2004; Hinchliffe et al., 1998; Levin et al., 1981; Payne-Johnson, 1986). It is likely that this finding has to do with the executive demands placed on a participant in a verbal fluency task—particularly that of response selection (i.e., producing an item that fits the category or letter criterion, doesn't violate any rules, and has not been spoken before). Similar response selection demands exist in verb generation tasks, where the subject is asked to read a noun and respond with a verb that goes with the noun (e.g., what it does or what it is used for). Selectional demands are likely greater when the noun has multiple associated verbs (such as BOAT—row, float, drive, steer, fish, etc.) than when there is one prepotent response (BED—sleep), and healthy controls do respond slower and less accurately to multiple-response nouns (Chiarello, Kacinik, Shears, Arambel, Halderman, & Robinson 2006). No visual field asymmetry was found in that study for many-response items, but there was a right visual field advantage for single-response items.

In order to see if these selection demands affect people with TBI in the same way as controls, a replication of the first experiment of Chiarello et al., 2006 was performed. It was hypothesized that the control group would show the same results as in the replicated study. The TBI group was expected to be preferentially sensitive to the one/many manipulation. It was also thought that they would show atypical lateralization effects that suggest abnormal control of language.

3.2 METHOD

3.2.1 Participants

The same 38 participants as described under Experiment 1, above, also participated in this experiment. Refer to Table 2.1 for participant information. The data from one person with TBI (206) had to be excluded because he consistently read the word on the screen aloud before generating a verb, thus rendering his vocal latency data unusable.

3.2.2 Materials and Design

Materials were taken from Chiarello et al. (2006—originally from Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and consist of sets of nouns which have been normed to have either a single dominant verb response or multiple possible verb responses. The words are all 3-6 letter concrete nouns, and the lists for single- and many-response items, as well as words presented to the right and left visual field, are matched for frequency, imageability, and length (see Table 3.1 for more information). Items from the two lists were presented in randomized order, with half the subjects seeing any particular item in the right visual field and half seeing it in the left. Items are collected in Appendix C.

Table 3.1 Descriptive Statistics for Items from Experiment 2

Measure	Left in List A, M (SD)	Right in List A, M (SD)	t-tests
Familiarity*	515.61 (145.28)	517.70 (166.20)	t(45) = -0.062, p = 0.95
Imageability	523.67 (188.04)	539.76 (172.18)	t(45) = -0.40, p = 0.69
Frequency	58.70 (81.22)	53.30 (59.32)	t(45) = 0.38, p = 0.71
Length (# letters)	4.33 (0.84)	4.39 (0.93)	t(45) = -0.38, p = 0.71
Length (# phonemes)	3.48 (0.69)	3.46 (0.81)	t(45) = 0.14, p = 0.89
Length (# syllables)	1.15 (0.36)	1.30 (0.51)	t(45) = -1.73, p = 0.09

Measure	One M(SD)	Many M(SD)	t-tests
Familiarity	520.57 (147.31)	512.74 (164.22)	t(45) = 0.24, p = 0.82
Imageability	534.22 (171.03)	529.22 (189.40)	t(45) = 0.12., p = 0.90
Frequency	53.43 (55.40)	58.57 (83.95)	t(45) = -0.38, p = 0.70
Length (# letters)	4.26 (0.88)	4.46 (0.89)	t(45) = -1.07, p = 0.29
Length (# phonemes)	3.41 (0.75)	3.52 (0.75)	t(45) = -0.66, p = 0.51
Length (# syllables)	1.26 (0.49)	1.20 (0.40)	t(45) = 0.65, p = 0.52

* Familiarity, imageability, and frequency counts were obtained from the MRC Psycholinguistic Database: Machine Usable Dictionary Version 2.00 (http://www.psy.uwa.edu.au/mrcdatabase/mrc2.html). Familiarity and imageability are based upon three merged sets of norms (see Appendix 2 of the MRC Psycholinguistic Database User Manual (Coltheart, 1981) for more details), and range from 100-700. Frequency is based on the Kucera and Francis written frequencies (Kucera & Francis, 1967).

A single trial includes a fixation cross alone for 800 msec (again with black-red-black "blink" at the end of that period to keep attention at center), then lateralized presentation of the word stimulus for 150 msec. The display parameters are repeated from Chiarello et al. (2006). A following fixation cross with a question mark (as in experiment 1) served as a probe screen, and was self-terminated, although subjects were instructed to respond as quickly as possible.

3.2.3 Procedure

The participants were again seated with their eyes 60 cm from the computer screen, and again asked to use the head-stabilizing device. Words appeared to one hemifield or the other, in capital letters subtending approximately 2 degrees of visual angle on average (dependent on word length), and were 1.65 degrees from fixation as in Chiarello et al. (2006). Following practice, all experimental trials were run in one block, and vocal latencies and responses were recorded to give measures of response time and accuracy. Instructions given to the participants were, "(to) produce a verb that goes with then noun you see. For instance, you could say what the noun is used for or what it does—just any verb that goes with that noun." Accuracy of response was coded by the experimenter, who sought multiple opinions if there was any question as to how a trial should be coded. Accuracy was coded liberally, with correct trials being reasonable verbs (in stem form or in any conjugation) for any of the possible senses of that noun. Trials necessitating other opinions were few in number, making up less than 1% of the total data set. Most answers judged as incorrect were non-verbs.

3.3 RESULTS

Reaction times where the participant failed to trigger the microphone with his or her first vocal response were removed from analysis. In addition, reaction times +/- 3SDs from each participant's mean (with 300 msec used as a lower bound where -3 SDs became a negative value) were trimmed to remove trials where subjects took unplanned breaks, etc. This latter reduction resulted in a loss of fewer than 2.5% of trials. Descriptive statistics are presented in Table 3.2. Reaction times from correct trials as well as percentage correct scores were subjected to 2 (response type) x 2 (visual field) repeated measures analyses of variance (ANOVAs). ANOVAs with the additional factor of group were also conducted to examine interactions with the other factors by group. All of these as well as planned contrasts and correlations with demographic variables are reported in the following sections.

Table 3.2 Descriptive Statistics, Experiment 2

Group	Condition	RT Mean (SD), msec	Accuracy Mean (SD), %
Control	Right, one	1202.97 (323.11)	90.12 (14.51)
	Right, many	1442.00 (352.50)	87.58 (17.52)
	Left, one	1277.10 (411.08)	89.59 (12.88)
	Left, many	1493.18 (339.73)	84.17 (22.91)
TBI	Right, one	1563.57 (569.75)	88.51 (13.71)
	Right, many	2069.33 (862.99)	82.49 (14.78)
	Left, one	1775.99 (823.38)	81.27 (18.15)
	Left, many	2046.28 (658.33)	76.97 (19.19)

3.3.1 Data from Controls

In the analysis of reaction times, there was a significant main effect of response type (F(1,18) = 18.768, p < 0.001), but no significant effect of visual field (F(1,18) = 2.538, p = 0.129) or response type by visual field interaction (F(1,18) = 0.042, p = 0.839). The effect of response type was such that “one” trials were responded to significantly faster than “many” trials. This effect can be seen in Figure 3.1.

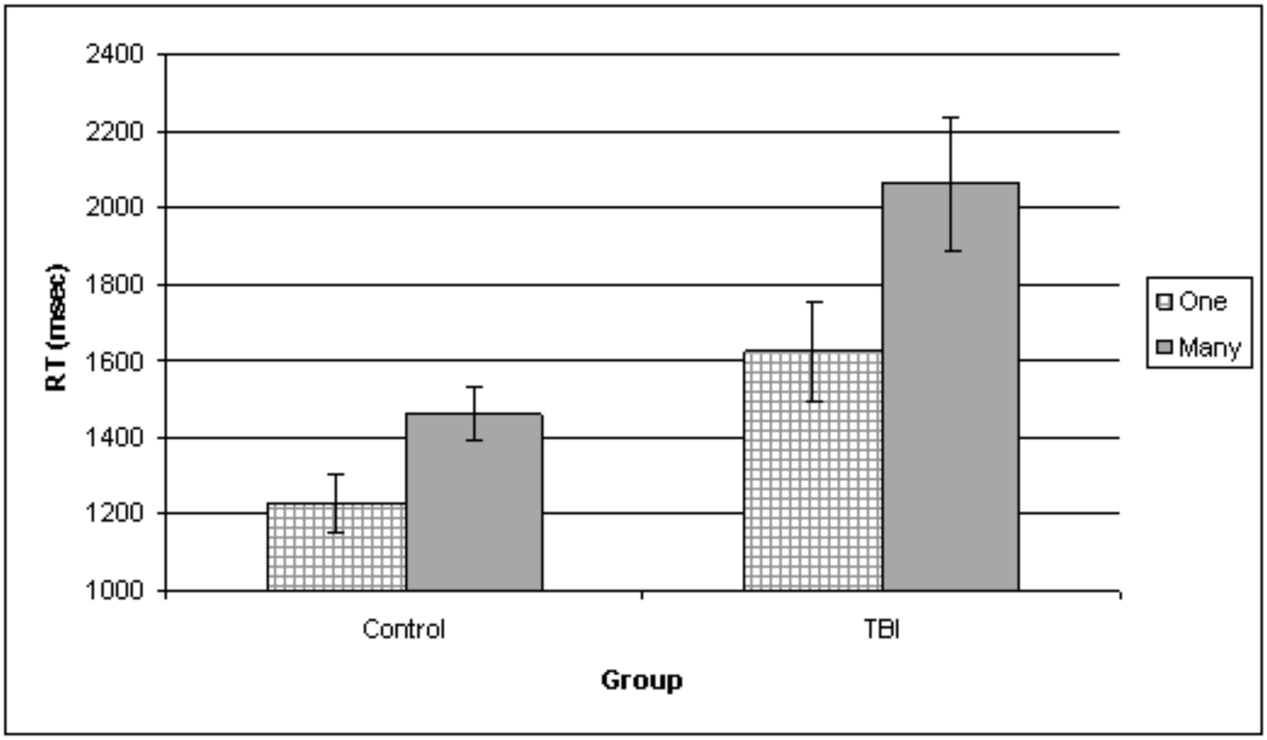

Figure 3.1 "One" trials are faster than "many" trials for both groups.

The accuracy analysis also suggested a difference for “one” and “many” trials, with the former producing relatively more accurate responses. There was, however, only a trend towards a main effect of response type in the analysis of accuracy F(1,18) = 3.900, p = 0.064. As the current sample of 19 control subjects is much smaller than Chiarello et al.'s (2006) sample of 68, it is likely this effect would pass statistical threshold levels with more participants. There was again no significant effect of visual field (F(1,18) = 0.910, p = 0.353), as well as no significant visual field by response type interaction (F(1,18) = 1.083, p = 0.312). Figure 3.2 provides a graphical view of these findings. Analyses by items for both RT and accuracy showed the same pattern of results—a main effect for response type (RT: F(1, 90) = 24.818, p < 0.0001; accuracy: F(1,90) = 5.353, p = 0.023) but no main effect of visual field (RT: F(1,90) = 1.197, p = 0.277; accuracy: F(1, 90) = 2.350, p = 0.129) or interaction (RT: F(1, 90) = 0.392, p = 0.533; accuracy: F(1, 90) = 0.528, p = 0.470). Planned comparisons were done to examine visual field effects for each response type in both the accuracy and response time data. None of these comparisons reached significance (all ps > 0.14).

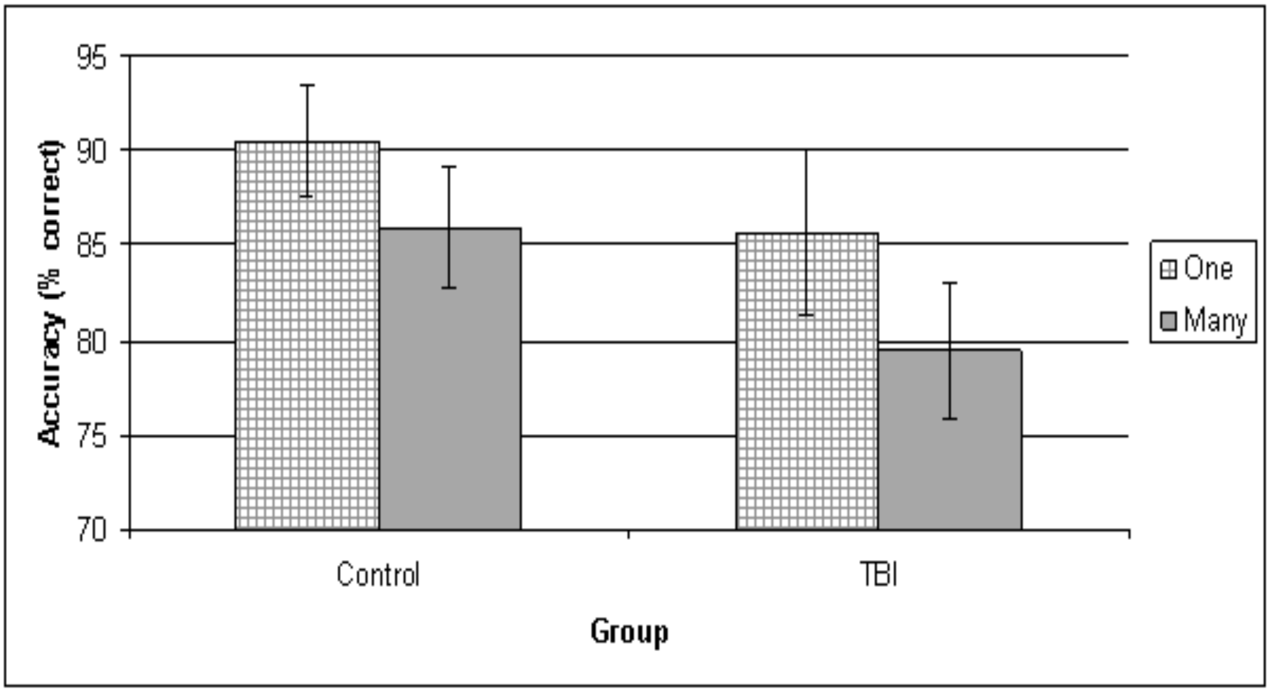

Figure 3.2 "One" responses are more accurate for both groups.

This pattern of effects and null results is very similar to what was found by Chiarello et al. (2006), in their study of non-injured subjects. In that study there were effects of response type as well, in the same direction, with no significant effect of visual field or visual field by response type interaction. They performed planned contrasts of the same type as in the current study but for RT data only as their measure of accuracy approached ceiling. In the "many" response category, they found no visual field asymmetry, but a right visual field advantage was found for the "one" category. The fact that the current study did not find this same advantage is likely due to issues of power and increased variance in a sample which included participants of a wide range of ages and education levels. Supporting this claim is the fact that the Chiarello et al. (2006) planned contrast finding reached significance with a 44 msec difference while in this study a difference of 74 msec between visual field means in the "one" condition (51 msec in the "many" condition) was found without significant result (refer to Table 3.3). Both differences were in the same direction, such that there was a benefit in reaction time to having seen a word in the right visual field.

Table 3.3 Planned Contrasts for Right Visual Field Effects by Group and Response Type

Group	Condition	Left minus right	t-tests (one-tailed)
Control	One (RT)	74.13 msec.	t(18) = 1.11, p = 0.14
	Many (RT)	51.18 msec	t(18) = 0.74, p = 0.24
	One (Accuracy)	-0.53 %	t(18) = -0.31, p = 0.38
	Many (Accuracy)	-3.41 %	t(18) = -1.11, p = 0.14
TBI	One (RT)	212.42 msec	t(17) = 1.61, p = 0.06
	Many (RT)	-23.05 msec	t(17) = -0.17, p = 0.43
	One (Accuracy)	-7.24 %	t(17) = -2.44, p = 0.01
	Many (Accuracy)	-5.52 %	t(17) = -1.89, p = 0.04

3.3.2 Data from People with TBI

The analysis of the data from the TBI group revealed a pattern of main effects and interactions similar to that found for controls. In the RT record, there was a significant main effect of response type (F(1, 17) = 26.246, p < 0.001), such that "one" trials were faster (see Figure 3.1). There was no significant main effect of visual field (F(1, 17) = 0.937, p = 0.347), and there was no interaction between the two factors (F(1, 17) = 1.645, p = 0.217. This same pattern held true in the analysis by items (response type: F(1, 90) = 20.800, p < 0.001; visual field: F(1, 90) = 0.059, p = 0.809; interaction: F(1, 90) = 1.220, p = 0.272).

In the accuracy data, there was again a significant main effect of response type such that "one" trials were more accurate (F(1, 17) = 11.195, p = 0.004). There was also not a significant interaction between response type and visual field (F(1, 17) = 0.148, p = 0.705. The factor of visual field did trend towards significance in this case, however (F(1, 17) = 3.113, p = 0.096), with responses to words presented in the right visual field being generally more accurate, as seen in Figure 3.3. The analysis by items again showed the same patterns as in the analyses by subjects. There was a significant main effect of response type (F(1, 90) = 6.448, p = 0.013) and no significant interaction (F(1, 90) = 0.779, p = 0.380). In this case, however, the main effect of visual field did reach significance (F(1, 90) = 6.448, p = 0.013).

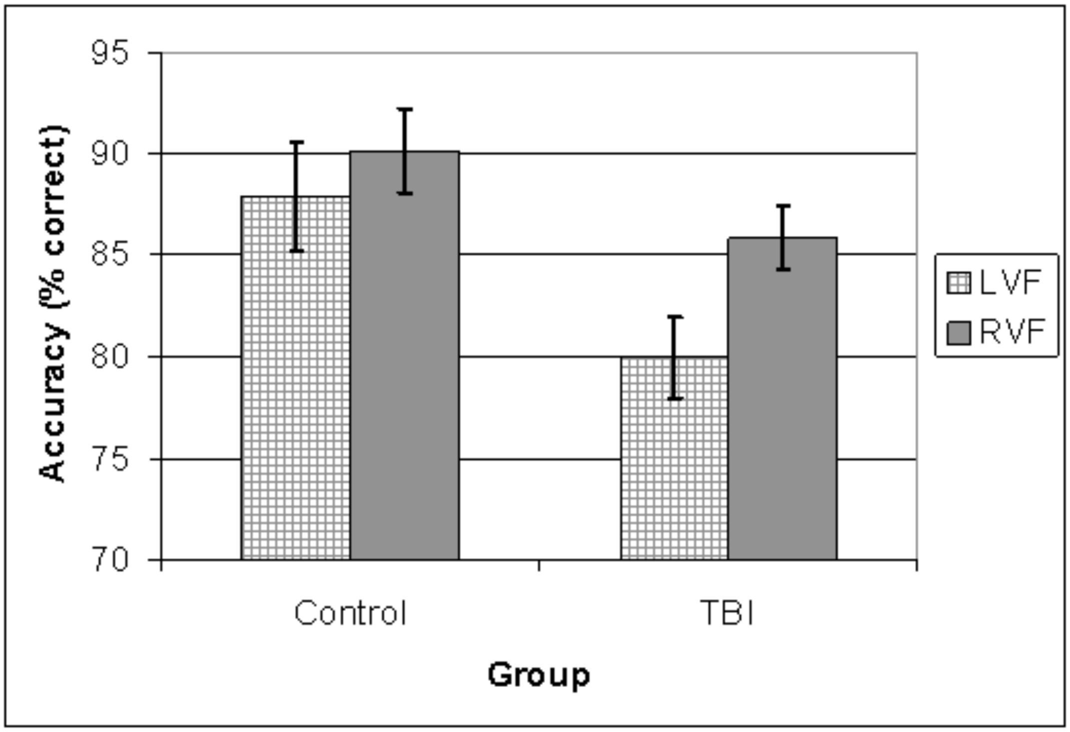

Figure 3.3 The TBI group shows a right visual field advantage, while controls do not.

Planned comparisons were again conducted looking for a right visual field advantage at each response type in both the accuracy and RT data (see Table 3.3). In contrast to the control data, many of these reached or neared significance. For accuracy, a right visual field advantage was found in both the "one" and "many" conditions such that seeing a word presented in the right visual field was associated with greater accuracy (one: t(17) = -2.445, p = 0.013; many: t(17) = -1.890, p = 0.038). Response time data showed a trend towards a right visual field advantage for the "one" condition only (one: t(17) = 1.609, p = 0.063; many: t(17) = 0.169, p = 0.434). This latter finding is similar to that found by Chiarello et al. (2006), who also found that their participants exhibited a visual field advantage in response time for the "one" condition only. On the whole, these results from the TBI group suggest that they are also sensitive to the one/many manipulation, and that they may be receiving a greater benefit (at least to accuracy) from viewing an item in the right visual field.

Turning to the analyses with group as a factor, we can now see how the manipulated variables may interact with group status.

3.3.3 Group Differences

Repeated measures ANOVAs were conducted on the response time and accuracy data with group (control, TBI), visual field (right, left), and response type (one, many) as factors. In the analysis of RT data by subjects, the main effect of response type was again significant (F(1, 35) = 45.421, $p < 0.001$), such that words with one typical answer were responded to faster. There was also a significant group effect, such that controls responded faster than people with TBI (F(1, 35) = 9.218, $p = 0.005$). There was a trend towards an interaction between response type and group such that the TBI group was disproportionately slower on “many” trials (F(1, 35) = 3.087, $p = 0.088$). There were no other significant main effects or interactions (visual field: F(1, 35) = 2.316, $p = 0.137$; visual field x group: F(1, 35) = 0.096, $p = 0.759$; visual field x response type: F(1, 35) = 1.484, $p = 0.231$; visual field x response type x group: F(1, 35) = 1.004, $p = 0.323$).

The analysis of RT data by items revealed the same pattern of results, including significant main effects of response type (F(1, 90) = 25.960, $p < 0.001$) and group (F(1, 90) = 25.960, $p < 0.001$), and the same type of interaction between group and response type which, in this case, reached the threshold of significance (F(1, 90) = 4.044, $p = 0.047$; see Figure 3.4). There were again no other significant main effects or interactions (visual field: F(1, 90) = 0.825, $p = 0.366$; visual field x group: F(1, 90) = 0.177, $p = 0.744$; visual field x response type: F(1, 90) = 0.509, $p = 0.478$; visual field x response type x group: F(1, 90) = 1.274, $p = 0.262$).

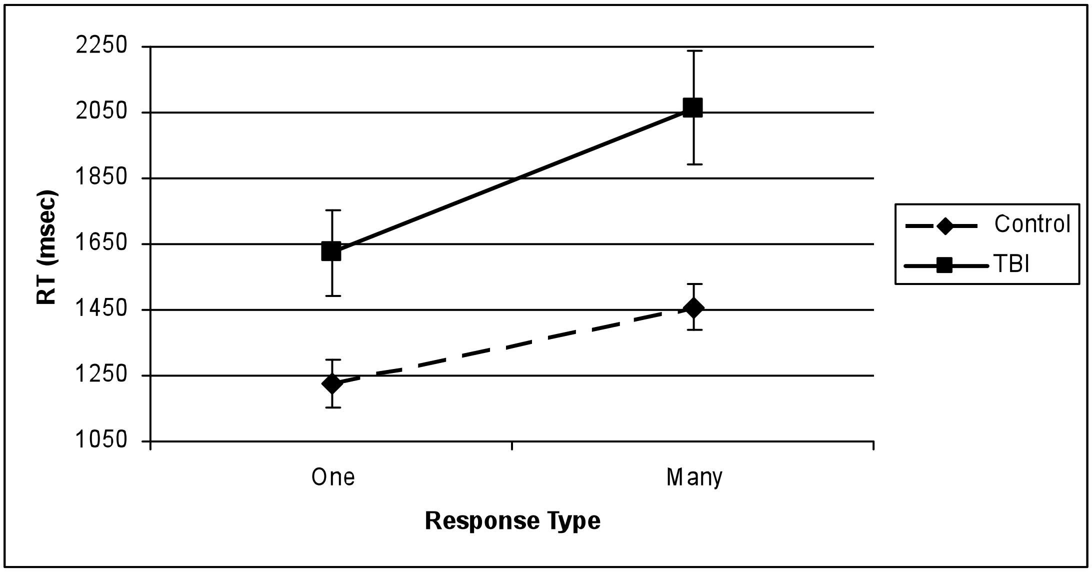

Figure 3.4 Reaction Times by Response Type and Group

The accuracy data, as analyzed by subjects, showed the same main effect of response type as previous analyses (F(1, 35) = 6.746, p = 0.014). In this case there was also a significant main effect of visual field such that responses made to words seen in the right visual field were more accurate (F(1, 35) = 8.771, p = 0.005). There was not a significant effect of group (F(1, 35) = 1.257, p = 0.270), and neither were there any significant interactions (response type x group: (F(1, 35) = 0.112, p = 0.740; visual field x group: F(1, 35) = 2.447, p = 0.127; visual field x response type: F(1, 35) = 0.049, p = 0.826; visual field x response type x group: F(1, 35) = 0.782, p = 0.383). The analysis by items also revealed the significant main effect of response type (F(1, 90) = 11.168, p = 0.001), as well as the significant main effect of visual field (F(1, 90) = 7.697, p = 0.007). There was an additional finding in this analysis of a significant main effect of group (F(1, 90) = 32.073, p < 0.001), such that controls showed better accuracy overall. There were no significant interactions (response type x group: F(1, 90) = 2.355, p = 0.128; visual field x group: F(1, 90) = 2.020, p =

0.159; visual field x response type: F(1, 90) = 1.128, p = 0.291; visual field x response type x group: F(1, 90) = 0.146, p = 0.704).

Together, these results again confirm the importance of the response type variable seen above in the individual group analyses, but additionally show differences between controls and people with TBI. Generally, controls seem to be responding faster and more accurately than people with TBI. This result is expected, given that the participants with TBI have experienced a brain injury which has been shown in a multitude of studies to be associated with cognitive deficits. More interesting is the interaction of response type and group such that the TBI group was disproportionately slower at the “many” trials. This finding will be considered in more detail below.

3.3.4 Number of items attempted

An additional analysis was done to examine whether the number of items attempted varied by group, response type, or visual field. There was a main effect for visual field, such that more items were attempted when seen in the right visual field than the left (F(1, 35) = 10.089, p = 0.003). There were no other significant main effects or interactions (response type: F(1, 35) = 0.131, p = 0.720; group: F(1, 35) = 0.005, p = 0.941; visual field x response type: F(1, 35) = 1.204, p = 0.280; visual field x group: F(1, 35) = 0.166, p = 0.686; response type x group: F(1, 35) = 2.592, p = 0.116; visual field x response type x group: F(1, 35) = 0.273, p = 0.605).

3.3.5 Correlations with Demographic Variables

Correlational analyses were done to see if either the accuracy or response time data was being influenced by subject demographics. All participants were entered into correlations between age and education and percentage accuracy and response time. As is generally found and was found in Experiment 1, accuracy was affected negatively by age and positively by education level (age: $r(37) = -4.85$, $p = 0.002$; education: $r(37) = 0.443$, $p = 0.006$). Response times showed a negative correlation with education ($r(37) = -0.428$, $p = 0.008$), but no relation to age ($r(37) = 0.119$, $p = 0.483$). Score on the Edinburgh Handedness Inventory (i.e., strength of right-handedness) also did not correlate with either RT or accuracy (ps > 0.249). Upon consideration of the patient group only, injury variables were also analyzed in conjunction with RT and accuracy, but no significant correlations arose between the two dependent variables and time since injury or best GCS in 24 hours (all ps > 0.19). Initial GCS showed a trend towards correlation with the two dependent variables, such that lower GCS was somewhat associated with slower response times ($r (18) = -0.370$, $p = 0.131$) and poorer accuracy scores ($r (18) = 0.438$, $p = 0.069$).

3.4 DISCUSSION

Both groups showed the same basic effect of response type, such that when a word was associated with one prepotent response, it was responded to faster and with greater accuracy. This finding is expected, as it replicates the findings of the study the current investigation is based on (Chiarello et al., 2006). It further confirms that people in the TBI group do respond to language stimuli similar to their control counterparts. The fact that no significant main effect of visual field and no interaction between visual field and response type were seen in the control participant analysis also replicates their findings. A non-replication present in the control data was that there was not a right visual field advantage found in the planned comparisons for “one” trials only; in fact, none of the comparisons were significant for controls. This is likely due to reduced power and greater variance in the current study as compared to Chiarello et al. (2006). The TBI group differed from controls in that they did show a significant main effect of visual field in the accuracy analysis done by items, and a trend when done by subjects. Planned comparisons of these data revealed that the right visual field advantage for the TBI group was found for both response types in the accuracy data, and for "one" trials only in the response type data. This latter finding aligns well with the Chiarello et al., (2006) finding.

What these results suggest about a right visual field advantage is that, while healthy controls may show it under some circumstances, statistically, it is a small effect. Chiarello et al. (2006) were able to find it with 68 fairly homogenous subjects, but 19 relatively heterogeneous controls were too few to bring the effect to significance. The TBI group when analyzed alone did show an effect of visual field in most cases, and even in cases where control subjects would not be expected to show it (i.e., for accuracy in the "many" trials). This finding suggests again that people with TBI may have benefits for viewing language stimuli in the right visual field, but may also go beyond that to suggest an abnormal benefit that might indicate disordered hemispheric communication.

The other notable finding is that, in the analyses with group as a factor, there is not only the expected main effect of group such that the control subjects are faster and more accurate than the participants with TBI, but there is also an interaction between group and response type such that TBI subjects are disproportionately worse on the "many" trials. As the "many" trials are the ones where subjects may need to choose between several possible competing responses, this interaction may reflect a particular deficit in an area where executive skill must interact with language. Together with the findings from Experiment 1, there is evidence that deficits in executive functioning are leading to problems with language processing. What now remains is to examine the underlying mechanisms for this influence. Experiment 3, a first pass at an analysis of functional connectivity on resting-state fMRI data, represents a beginning in this direction.

4.0 EXPERIMENT 3

4.1 INTRODUCTION

Though cognitive neuroscience sometimes seems to be concentrating on what single brain areas "do," much of it is really concerned with how brain areas interact. Historically, the discussion of this question has been based on the actual physical connections between neurons in different areas of interest, a line of investigation that continues to this day. With the advent of neuroimaging techniques, however, another method for examining interaction of brain areas has arisen—that of functional connectivity. Functional connectivity analyses use cross-correlations between timecourses of activity in separate brain regions that are thought to have some functional relationship (e.g., Biswal, Yetkin, Haughton, & Hyde, 1995; Friston, 1994). Originally done with resting-state data, these correlations are thought to represent relationships between brain regions, without really commenting on how these are mediated.

While some research groups are now using data collected during a cognitive task to do these computations (e.g., Rissman, Gazzaley, & D'Esposito, 2004), resting-state analyses are still quite common. They not only are an economical alternative, as many fMRI experiments include some time where the participant is at rest, but they also avoid confounds arising from how the task chosen affects the brain areas of interest (Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002). One group has examined how different configurations of rest conditions (single continuous rest block, rest blocks alternated with task, and resting time segments taken from an event-related design) affect this resting-state analysis of functional connectivity (Fair et al., 2007). What they found was that analyses carried out on the two kinds of blocked designs were very similar, but that analyses on event-related data showed quantitative differences and should be interpreted carefully. The first of these findings is directly relevant to the current study, as it will be conducted on blocks of rest data which flank task blocks.

The other way functional connectivity analyses have differed is in their approach to parceling the brain, similar to the way functional MRI data are handled. Some researchers use a voxel-based analysis in which a seed (voxel or region of interest—ROI) is compared to each other brain voxel for connectivity. The current study takes a second, ROI-based approach, in which only correlations between different regions are computed. In this case, the areas of interest are areas that have traditionally been implicated in language tasks or in executive control tasks. Two from each literature (see review sections, above) were chosen. These included (inferior frontal gyrus (IFG) and superior temporal gyrus (STG) for language; dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) for executive functioning). As this study is a small-scale study on pilot data, it was thought that choosing large, somewhat nonspecific areas, especially in the language domain, might help with issues of power and lead to greater ability to generate more specific ROI hypotheses in future studies. To address questions of inter-hemispheric functional connectivity and difference in this between the groups, both the left and right homologue of each of these areas was used in the analysis—yielding eight total regions of interest. Comparisons were made between each of these areas, and special attention was paid to connectivity between language and executive areas, as well as differences between inter- and intra-hemispheric values.

While it should be restated that functional connectivity data remains silent on how these correlations between areas are mediated neurally (Friston, 1994), if there is disruption on the neural side, it might be expected that functional connectivity might be negatively affected. Since we are dealing here with an injury that frequently affects the corpus callosum, it was hypothesized that the TBI group would show reduced connectivity as compared to controls, especially for areas that were in contralateral hemispheres.

4.2 METHOD

4.2.1 Participants

Participants were 5 controls and 5 persons with TBI (all male) who participated in an fMRI pilot experiment in our lab. Inclusion and exclusion criteria for this study were the same as described above, with the addition of MRI safety exclusion criteria. Four of the people with TBI and three of the controls also participated in experiments 1 and 2. Age of the control group averaged 42 years (SD = 11.6, range = 26-53) and the TBI group average for age was 43.6 years (SD = 11.0, range 26-55). Mean number of years of education was 14.8 for the control group (SD = 2.7, range 12-18), and 16 years (SD = 2.4, range = 12-18), for the TBI group. Age and education levels were thus not significantly different between the groups (age: t(4) = -0.98, p = 0.38; education: t(4) = -1.5, p = 0.21). All five participants with TBI sustained injuries graded as severe by initial GCS (M = 3.8, SD = 1.8, range 3-7), but nearly all were given paralytic medication and breathing assistance, which can potentially produce artificially low GCS scores. Best GCS scores in the first 24 hours showed some improvement (M = 9.4, SD = 2.2, range 7-11). Even based on these scores, however, at least moderate injury was still measured for all participants. An average of 1.6 years had elapsed from time of injury to time of testing (SD = 0.7, range = 1.03-2.57). Table 4.1 collects these and other participant demographics.

Table 4.1 Participant Demographic Information, Experiment 3

Subject	Match	Sex	Age	Education	Initial GCS	Best GCS in 24 hrs	Time post-injury (yrs)	Etiology	TBI Type
101	201	M	51	12					
102	206	M	34	18					
103	207	M	26	16					
104	205	M	46	16					
106	204	M	53	12					
201	101	M	48	12	3 TP	7	1.87	MVA	SAH
205	104	M	48	16	3 TP	11	2.57	MCA	SDH, EDH, SAH
206	102	M	41	18	7	11	1.27	Falling object	IPH/HC & SDH
207	103	M	26	18	3 TP	11	1.03	Fall	SDH, SAH, HC
204	106	M	55	16	3 TP	7	2.17	MCA	SAH & IPH

Abbreviations: GCS = Glasgow Coma Score, T = intubated, P = given paralytic medication, MCA = motorcycle accident, MVA = motor vehicle accident, SAH = subarachnoid hemorrhage, IPH = intraparenchymal hemorrhage, SDH = subdural hemorrhage, HC = hemorrhagic contusion, EDH = epidural hemorrhage

4.2.2 Materials and Design

Data for this investigation was taken from the rest periods of an fMRI experiment using spatial and verbal versions of an N-Back paradigm. Six experimental runs were collected for each participant, and the rest periods were comprised of the first and last 20 seconds of each run. Resting-state data for each participant was concatenated, and the first 8 seconds (4 volumes) for the second rest period in each scan were removed as it represented a period following a task and the hemodynamic response was likely still elevated due to task-related activation. While 8 seconds is less than the typically described amount of time it takes for the hemodynamic response to return to baseline (estimates range from 10-18 seconds depending on stimulus presentation, e.g., Wager, Hernandez, Jonides, & Lindquist, 2007:36), it was necessary to compromise between the number of volumes removed and the total number of volumes used.

4.2.3 fMRI Procedure

Scans were conducted on a 3-Tesla head-only Siemens Allegra magnet at the University of Pittsburgh and Carnegie Mellon University's joint Brain Imaging Research Center (BIRC). Foam padding was used to minimize head movement. Scanning parameters for the EPI images were typical for the center at the time of project development (TE = 25 ms, TR = 2000 ms, FOV = 200 mm, flip angle = 79 degrees, number of slices = 39, slice thickness = 3 mm, skip = 0). Structural scans and a DTI sequence were also collected during each session, for use in the original study. All participants signed informed consent approved by the University of Pittsburgh's Institutional Review Board before beginning.

4.2.4 Analysis Procedure

As part of the original project, the entire data set for each participant underwent preprocessing with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Motion correction, coregistration, and normalization to the MNI template were conducted. The normalized versions of the images were used in this analysis.

As described above, each participant experienced six runs, each with 20 seconds of rest at the beginning and ending of the run. The first 20 seconds (10 volumes) and the last 12 seconds (6 volumes) of each run were concatenated, yielding a total of 96 volumes per participant. The ROIs of interest were defined for each person using the Wake Forest University Pickatlas (http://fmri.wfubmc.edu/cms/software#PickAtlas; Maldjian, Laurienti, Burdette, & Kraft, 2003) to create mask files. Separate masks were made for each ROI in each hemisphere, yielding a total of 8 mask files. Copies of these mask files were then coregistered to each participant's own normalized functional data. The functional connectivity analysis was conducted using the REST toolkit (http://resting-fmri.sourceforge.net/). Analysis began with linear detrending, and the default band pass filter (0.01 ~ 0.08 Hz) was applied. Connectivity values between the 8 ROIs (left and right homologues of the four areas described above) were then computed. These values were then compared with standard statistical analyses, described below.

4.3 RESULTS

Connectivity values were obtained between the 8 areas of interest, such that a matrix with 28 unique connection values was generated. Values for each of these for each of the two groups can be viewed in Table 4.2. Paired t-tests were done on each of these 28 connection values for the TBI and control groups. Of these, only two approached significance, that for the connection between the right ACC and the right DLPFC (t(4) = -2.21, p = 0.09), and that for the connection between the right ACC and the left STG (t(4) = -2.33, p = 0.08). These comparisons were, however, not in the direction we had originally hypothesized. Instead, both comparisons demonstrate a higher level of functional connectivity for the TBI group than controls; for this reason, a qualitative examination of this pilot data was conducted. The comparisons which evidenced larger (albeit not significantly so) values for the TBI group than the control group mainly included connections involving the right and left anterior cingulate areas (13 comparisons, see Table 4.3).

Table 4.2 List of all Examined Connectivity Points

Connection	Control M (SD)	TBI M (SD)	t-test
L & R ACC	0.937797 (0.04)	0.946059 (0.05)	t(4) = -0.37, p = 0.73
L & R DLPFC	0.921068 (0.04)	0.879801 (0.09)	t(4) = 1.51, p = 0.21
L & RIFG	0.932505 (0.06)	0.901750 (0.11)	t(4) = 0.48, p = 0.65
L & RSTG	0.952457 (0.03)	0.940705 (0.05)	t(4) = 0.49, p = 0.65
L ACC & L IFG	0.837223 (0.13)	0.901775 (0.06)	t(4) = -0.91, p = 0.42
L ACC & L DLPFC	0.790611 (0.14)	0.879260 (0.08)	t(4) = -1.81, p = 0.14
L ACC & L STG	0.775957 (0.14)	0.837381 (0.10)	t(4) = -1.07, p = 0.34
R ACC & R IFG	0.835549 (0.13)	0.907278 (0.03)	t(4) = -1.25, p = 0.28
R ACC & R DLPFC	0.720353 (0.22)	0.894108 (0.07)	t(4) = -2.21, p = 0.09
R ACC & R STG	0.707607 (0.21)	0.832385 (0.11)	t(4) = -1.92, p = 0.13
L ACC & R IFG	0.842416 (0.13)	0.896775 (0.03)	t(4) = -0.81, p = 0.46
L ACC & R DLPFC	0.730139 (0.19)	0.877226 (0.05)	t(4) = -1.92, p = 0.13
L ACC & R STG	0.760724 (0.18)	0.847654 (0.08)	t(4) = -1.46, p = 0.22
R ACC & L IFG	0.817656 (0.14)	0.884556 (0.07)	t(4) = -1.12, p = 0.32
R ACC & L DLPFC	0.739034 (0.18)	0.829557 (0.19)	t(4) = -1.43, p = 0.23
R ACC & L STG	0.734321 (0.17)	0.844062 (0.10)	t(4) = -2.33, p = 0.08
L IFG & L DLPFC	0.921202 (0.04)	0.895594 (0.11)	t(4) = 0.69, p = 0.53
L IFG & L STG	0.926701 (0.04)	0.921979 (0.08)	t(4) = 0.15, p = 0.89
R IFG & R DLPFC	0.850846 (0.10)	0.908513 (0.05)	t(4) = -1.68, p = 0.17
R IFG & R STG	0.877830 (0.09)	0.895523 (0.09)	t(4) = -0.45, p = 0.68
L IFG & R DLPFC	0.830387 (0.09)	0.859014 (0.11)	t(4) = -1.12, p = 0.33
L IFG & R STG	0.916437 (0.05)	0.921127 (0.07)	t(4) = -0.15, p = 0.89
R IFG & L DLPFC	0.870968 (0.07)	0.871684 (0.17)	t(4) = -0.01, p = 0.99
R IFG & L STG	0.869049 (0.08)	0.860621 (0.11)	t(4) = 0.16, p = 0.88
L DLPFC & L STG	0.871629 (0.06)	0.792813 (0.24)	t(4) = 0.77, p = 0.49
R DLPFC & R STG	0.788685 (0.12)	0.790100 (0.14)	t(4) = -0.06, p = 0.95
L DLPFC & R STG	0.860821 (0.08)	0.854808 (0.19)	t(4) = 0.11, p = 0.92
R DLPFC & L STG	0.799331 (0.11)	0.797120 (0.13)	t(4) = 0.07, p = 0.95

Table 4.3 Qualitative Description of the Data

Greater for Controls	Greater for TBI Group
L & R DLPFC	L & R ACC
L & R IFG	L ACC & L IFG
L & R STG	L ACC & L DLPFC
L IFG & L DLPFC	L ACC & L STG
L IFG & L STG	R ACC & R IFG
R IFG & L STG	R ACC & R DLPFC
L DLPFC & L STG	R ACC & R STG
L DLPFC & R STG	L ACC & R IFG
R DLPFC & L STG	L ACC & R DLPFC
	L ACC & R STG
	R ACC & L IFG
	R ACC & L DLPFC
	R ACC & L STG
	R IFG & R DLPFC
	R IFG & R STG
	L IFG & R DLPFC
	L IFG & R STG
	R IFG & L DLPFC
	R DLPFC & R STG

In fact, all comparisons between the ACC and other areas were larger for the TBI group. The other values larger for the TBI group included more connections within the right hemisphere, as well as a few interhemispheric connections. Controls, on the other hand, showed larger values for more self-connected homologues (3 of 4), as well as more connections involving at least one left hemisphere area.

The original 28 comparisons were then further coded for three factors: hemisphere type (whether the connection crossed to the contralateral hemisphere or not), connection type (whether it connected right and left hemisphere homologues of the same area or two different areas), and hemisphere (for connections that stayed within one hemisphere, coded for right or left). Paired-samples t-tests were computed for each connection, as well as for each of the three recoded factors, to see if the control group or the patient group showed a higher degree of functional connectedness. Most of these comparisons did not reach significance (see Table 4.4), but the comparison between groups of connectivity values for areas within the right hemisphere was significant (t(4) = -2.78, p = 0.05). Again, the TBI group exhibited a higher degree of connectivity (M, control: 0.797, SD = 0.12; M, TBI: 0.871, SD = 0.075). Paired t-tests were then run on each matched pair of participants to see if certain pair groups were biasing these results. For the older two pairs of participants, there was no difference in a total measure of functional connectivity between the patient and control of the matched pair. Of the remainder, one pair which unfortunately included a rather younger control was barely significant such that the control exhibited greater functional connectivity, but two pairs were highly significant with the TBI member showing greater values (see Table 4.4).

Table 4.4 Matched Pair Comparisons

Comparison	Control M (SD)	TBI M (SD)	t and p values
101 & 201	0.82 (0.11)	0.82 (0.08)	t(27) = 0.16, p = 0.87
102 & 206	0.97 (0.02)	0.96 (0.03)	*t(27) = 2.10, p = 0.05
103 & 207	0.78 (0.12)	0.91 (0.06)	*t(27) = -5.15, p < 0.001
104 & 205	0.88 (0.06)	0.93 (0.04)	*t(27)= -5.57, p =< 0.001
106 & 204	0.73 (0.15)	0.76 (0.13)	t(27) = -0.80, p = 0.43
Same Area	0.94 (0.03)	0.92 (0.07)	t(4) = 0.72, p = 0.51
Different Area	0.82 (0.10)	0.87 (0.09)	t(4) = -1.79, p = 0.15
Contralateral	0.84 (0.09)	0.88 (0.08)	t(4) = -1.26, p = 0.28
Ipsilateral	0.83 (0.10)	0.87 (0.09)	t(4) = -1.82, p = 0.14
Left	0.85 (0.08)	0.87 (0.07)	t(4) = -0.65, p = 0.55
Right	0.79 (0.12)	0.87 (0.07)	*t(4) = -2.78, p = 0.05
Total	0.84 (0.09)	0.87 (0.08)	t(4) = -1.51, p = 0.21

Repeated measures ANOVAs were then performed on the data by group separately for each of the three factors described above. For the ANOVA describing the relationship between hemisphere type (contralateral, ipsilateral), and group, the factor of hemisphere type was significant such that there were greater functional connectivity values for contralateral connections (F(1, 8) = 10.006, p = 0.013). The factor of group was not significant (F(1, 8) = 0.464, p = 0.515), but the interaction between the two approached significance (F(1, 8) = 3.973, p = 0.081). This interaction is such that, while both groups show greater connectivity for contralateral connections than ipsilateral connections, this difference is less pronounced for the TBI group (see Figure 4.1).

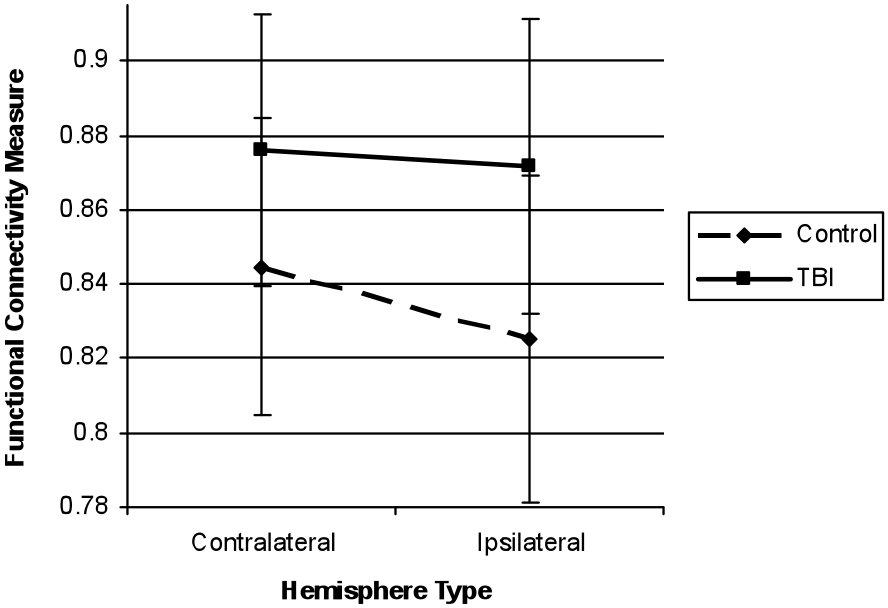

Figure 4.1 Functional Connectivity by Hemisphere Type and Group

For the connection type factor (same area on both sides, two different areas), connection type was significant such that functional connections between the same area on both sides were stronger (F(1, 8) = 18.823, p = 0.002). There was not a significant group effect (F(1, 8) = 0.095, p =

0.766) or an interaction (F(1, 8) = 2.937, p = 0.125). The ANOVA for hemisphere (right, left) by group also did not show a significant group effect (F(1, 8) = 0.605, p = 0.459). The effect of hemisphere approached significance (F(1, 8) = 3.134, p = 0.115), as did the hemisphere by group interaction (F(1, 8) = 3.101, p = 0.116). The direction of these trends showed that overall, connectivity was greater on the left than the right, and that this effect was driven by the control group, which showed much less connectivity on the right while the patient group had similar connectivity values for both sides (see Figure 4.2).

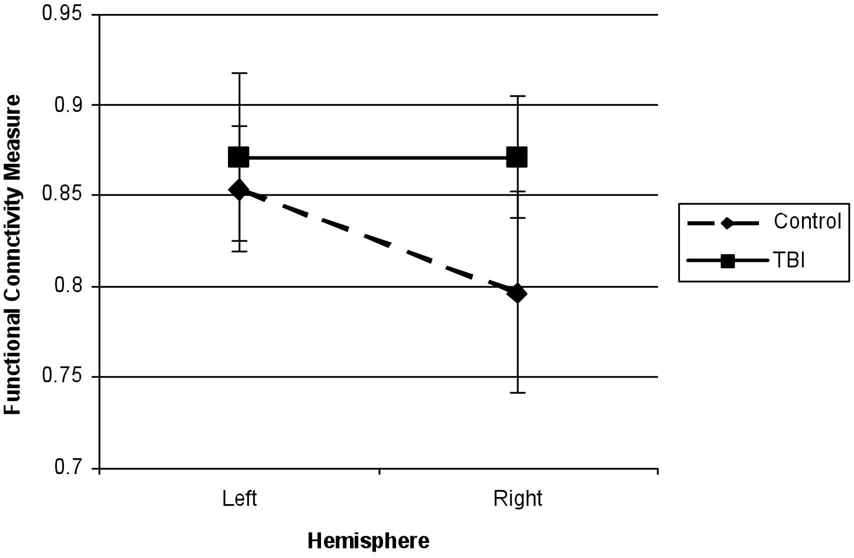

Figure 4.2 Pattern of Functional Connectivity by Hemisphere and Group

Because our sample was rather divergent on age and number of years of education, correlations between the functional connectivity factors described above and those two demographic factors were also calculated. Based on the characteristics of the matched pair comparisons described above, it might be expected that age would be significantly correlated, but it was actually not significantly correlated with any factor (see Table 4.5). Education, however, was significantly or nearly significantly positively correlated with all factors (also detailed in Table 4.5). These correlations suggest that our participants with higher education levels also displayed higher levels of functional connectivity.

Table 4.5 Correlational Analysis

Measure	Age (p val)	Education	Initial GCS	Best 24	Time Since
Total	-0.407 (0.243)	*0.694 (0.026)	0.552 (0.334)	*0.946 (0.015)	-0.329 (0.588)
Different Area	-0.402 (0.250)	*0.685 (0.029)			
Same Area	-0.358 (0.310)	0.615 (0.059)			
Contralateral	-0.376 (0.284)	*0.679 (0.031)			
Ipsilateral	-0.442 (0.201)	*0.709 (0.022)			
Left	-0.408 (0.241)	0.588 (0.074)			
Right	-0.436 (0.208)	*0.757 (0.011			

Finally, in order to determine if there were any features of injury which correlated with higher functional connectivity values, correlational analyses were run between a total measure of functional connectivity (averaged across all 28 comparisons) and initial GCS, best GCS in 24 hours, and time since injury (Table 4.5). Of these, only best GCS in 24 hours was significantly correlated (r(5) = 0.946, p = 0.015).

4.4 DISCUSSION

The set of pilot data analyzed in this section for functional connectivity is obviously too limited to allow strong conclusions to be drawn, but there are some findings worth investigating further. The original hypothesis was dependent on an idea that, with disturbed white matter connectivity, there might be similarly disrupted functional connectivity. It was not necessary that this be true, however, and it does not seem to be the case here. Contrary to the original hypothesis, the overarching theme of these findings is that the patient group has, at rest, a higher degree of functional connectivity between brain areas involved in language and executive functioning than controls. This higher degree of connectedness is especially evident on connections within the right hemisphere, as well as links between the anterior cingulate cortex and other areas. The difference for right hemisphere involvement functionally is consistent with imaging studies, discussed in the introductory sections of this work, that showed greater right hemisphere activation in PET and fMRI studies of cognition after traumatic brain injury (Christodoulou, et al., 2001; Newsome, et al., 2007; Ricker, et al., 2001; Turner & Levine, 2008). The latter of these findings, i.e., higher connectedness with the ACC for the patient group, is interesting and should be considered in more detail.

The anterior cingulate has been a target of much research over the past several years, and there have been many theories put forth as to its function. Probably the two most influential of these have been that it is involved in conflict monitoring (e.g., as reviewed in Carter & van Veen, 2007), or error detection (reviewed in Paus, 2001). Extensions of these have been discussed as well, for example, Botvinick (2007) has suggested that beyond just monitoring conflict, the ACC then uses that information to modulate cognitive control. Finally, it has been mentioned that the ACC is situated in a particularly interesting region in the brain with local connections to cognitive, motor, and physiological arousal areas, and that integration of these is likely to be an important function of the ACC as a whole. As such, Paus (2001) notes that neural activity in the ACC seems to be modulated by task difficulty, with tasks that are more difficult being associated with a greater arousal/stress response. When considering these theories of ACC function in conjunction with the current finding for increased ACC connectivity for patients, a compensatory effect is suggested—

i.e., that people in the TBI group are trying to keep tighter cognitive control or having to work harder (having greater arousal, perhaps in response to finding tasks more difficult than others do).

Speculation on these findings together might suggest that having a more tightly coupled system functionally might be adaptive after injury. Since this was found during resting activity, it is possible either that a) rest represents less of a “true rest” in the patient group (i.e., they are engaging in some extra processing either for task readiness or because there is extra processing associated with resting for them) or b) this higher level of coupling might scale up and be additionally seen during task blocks. Future studies extending the functional connectivity analysis to both task and rest epochs will illuminate whether having higher functional connectedness values in fact translates to having continued high values during cognition, and finally whether this results in better task performance.

The single study currently in the literature examining issues of functional connectivity after TBI did find lower functional connectivity in patients as compared to controls for their areas of interest only during a condition where there was directed semantic analysis and memory (Strangman et al., 2009). As they did not also do an analysis of the resting-state data, and as their population has a much longer time since injury (M = 14.1 years, SD = 10.2 years), it is not clear how to relate their study to the current one. It is possible that functional connectivity values are high closer to the time of injury and lower later, that there are interactions with age as suggested by the current findings, or that lower values would be found during any task with the same kind of situation they produced. More work must be done to separate these possibilities.

While not much information exists on functional connectivity after TBI, there are some works in the literature on other disorders with neurological influence which would add support to the idea that there can be an increase in functional connectivity even when the brain is compromised. For example, Noonan, Haist, & Müller (2009) examined 10 persons with and 10 without Autism Spectrum Disorder (ASD) with fcMRI obtained during a cognitive task, and found that their participants with ASD demonstrated a more extensive pattern of functional connectivity, though previous studies (also reviewed by Noonan et al., 2009) have found reduced white matter integrity in ASD. Similar results have been obtained in schizophrenia research, where many investigators have found increased functional connectivity in people with schizophrenia, though others have not (see Greicius, 2008, for a review). One study which did report increased connectivity in people with schizophrenia described a widespread connectivity map in that group as compared to a more focused map for controls (Boksman et al., 2005). Finally, while studies on normal aging have typically found reductions in functional connectivity for older adults (e.g., Wu et al., 2007), one study has found that even when there is reduced connectivity between some brain areas, there can be other areas of enhancement in functional connectivity. St. Jacques, Dolcos, & Cabeza (2009) found older adults to have reduced functional connectivity between the amygdala and the hippocampus, but increased functional connectivity between the amygdala and the DLPFC, suggesting that older adults may have greater regulation of emotional responses. As memory performance was poorer in the older adults, it is possible this increased regulation is an attempt to improve functioning. In sum, these studies investigating functional connectivity in aging, schizophrenia, and ASD are suggestive that 1) full white matter integrity is not necessary for increases in functional connectivity, and 2) that there are situations in which patient populations can exhibit increased functional connectivity, which in some cases may be in the service of compensatory efforts.

Future studies should further investigate whether there is a relationship between functional connectivity values and cognitive or functional outcomes. If such a relationship exists, future rehabilitation efforts could take this into account—providing patients with training likely to increase functional connectivity between areas of interest, if training can be found to do this reliably. Obviously this course represents a rather distant point in the future, but if it can be made to work it would be a natural outgrowth of studies like the current investigation.

Finally, it was also interesting to note that education correlated so consistently with the functional connectivity measures. The fact that the nature of these correlations was positive (more education is associated with higher connectivity values) is noteworthy, even though it is unclear what the underlying relationship is. It would be tempting to attribute neuroprotective properties to education, but a more likely relationship might revolve around the nature of the connections already existing in people who seek out further educational opportunities. Unfortunately resolving this question is outside the scope of the current study.

5.0 CONCLUDING REMARKS

Traumatic brain injury is a kind of injury to the brain that is commonly obtained through falls, assaults, and motor vehicle accidents, which disproportionately affects young males. Nearly 1.4 million people sustain a TBI every year, and these can result in traumatic injury to axons, and to a lesser extent focal damage, especially in the brain's frontal and temporal poles. These injuries can lead to physical, psychological, and cognitive disturbances including difficulty with memory, speed of processing, executive functioning, and language.

The literature on language processing after TBI is ambiguous but the best summary would likely note that problems with discourse are commonly found, and lower level deficits are sometimes, but not consistently, seen. Executive functioning, on the other hand, is found to be impaired in nearly all studies examining it after TBI, regardless of testing method or task. It has been suggested, based largely on investigations of discourse or narrative, that executive functioning deficits may be the underlying cause of language problems. Data-driven demonstrations of this claim are noticeably lacking from the literature, however, which is where the current project began. The other piece of this investigation had to do with not only demonstrating an influence of executive control on language processing but then beginning to examine the mechanisms that make this possible. The network of brain areas that has been to date implicated in playing a role in executive functioning is extensive and distributed. Damage to connections between these areas is likely to occur with TBI. One particular area which is commonly affected by TBI is the corpus callosum. Because of these facts, the current series of projects began with two split visual field experiments designed to concurrently investigate potential influences of executive functioning on language processing as well as interhemispheric transfer issues. The final experiment was an analysis of resting-state fMRI data with the same goals in mind.

The first experiment used a standard paradigm of semantic priming with lexical decision. Related and unrelated experimental trials were presented on one side of visual space or the other. Filler trials of unrelated and related pairs as well as pairs in which the second word presented was a nonword were included to balance the percentage of related to unrelated trials, word to nonword trials, and presentation types for trials (same side, opposite sides, bilateral). While this study failed to replicate previous findings in the priming literature and had practice effects mar our ability to investigate the different percentages of related trials in a block, several interesting results did arise from it. General group differences were found such that controls were consistently faster and often more accurate. This is different from other language investigations we have done and may reflect the impact of speed of processing differences as seen during a fast-paced timed task. The fact that overall patterns of responding were similar for both groups would support that claim over one of generalized language difficulty.

As far as visual field differences were concerned, there was a slight benefit for accuracy when participants saw words in the right visual field. This finding is consistent with years of literature demonstrating a right visual field (left hemisphere) advantage for processing language stimuli. This benefit was found to be more prominently displayed in the TBI group than it was for the control group, perhaps suggesting either a greater reliance on the left hemisphere for language stimuli, or a general advantage for processing when it begins in the left hemisphere. Teasing apart these ideas is a target for future work, but as the second experiment also showed a RVF advantage in the TBI group but not in the control group, it does seem somewhat reliable.

A final issue addressed by this first experiment is the influence of executive functioning on language processing. There were two results which speak to this issue. First, trials where attention had to be switched from one side to the other were slower than trials where both words appeared one after the other on the same side. This finding is not interesting in and of itself as attention researchers have been demonstrating this result for decades. What is interesting is where the control and TBI groups differed—while both groups had a similar accuracy rate to "switch" trials, the control group did significantly better on "same" trials. This finding might suggest that having to switch attention on some trials is hurting the TBI group more. The other relevant finding has to do with the bilateral redundancy gain effect. In control participants from other studies, accuracy is found to be better and response times are similar (Mohr et al., 2000) or faster (Mohr et al., 2007) for trials presented bilaterally as compared to unilaterally presented trials. These results were replicated here in that both groups were more accurate in responding to bilaterally presented trials, and that control participants did not differ in mean response times to both kinds of trials. The TBI group, however, was slower to respond to bilateral trials than unilateral trials. This result has also been seen in the literature for people with compromised white matter (Mohr et al., 2000), though the non-control population in that study had schizophrenia, and not TBI. Regardless, this finding is suggestive that either a) hemispheric interaction is compromised and/or b) attention is compromised in this population. Since the latter is known to be true, but is not especially predictive in specific terms, it is the former idea for which evidence was sought in the remaining two studies.

With the second experiment, executive control was more directly manipulated in the form of selection demands in a verb generation task also presented using split visual field methodology with collection of vocal latencies (from Chiarello et al., 2006). For both groups in this study, words for which there were multiple potential good responses were responded to slower and less accurately than words which had one prepotent response. When data from the two groups was analyzed together, in addition to this main effect there was also an interaction such that the TBI group was disproportionately slow for trials with multiple responses. Since these trials are arguably more complex, this finding again provides evidence that it is especially under situations of complexity, or increased executive difficulty, in which problems are seen for language after TBI. What still has not been shown is how that is accomplished. According to Banich (1998, 2003), while a task may start out being processed in one hemisphere, the other hemisphere is additionally recruited during tasks of increased complexity. She posits this to be true even when it will result in a sacrifice in processing time, because the necessity for increased processing power is greater. Due to brain injury, the TBI group may have a lower threshold for recruiting that other hemisphere and increasing processing power, even though it does require more time to do so. While this idea is interesting, it is not yet clear whether there is disordered hemispheric communication in people with TBI.

That is where the third experiment, an analysis of resting-state fMRI data collected in an unrelated study, comes into play. Generally speaking, the patients showed a tendency towards higher functional connectivity values than controls. While this was only significant in three comparisons (right ACC & right DLPFC, right ACC & left STG, and connections between all right hemisphere areas), a qualitative look at the data shows many more comparisons leaning towards higher values for the TBI group. These clustered in a unique manner as well—with the comparisons benefiting the TBI group being nearly all related to the ACC, or involving the right hemisphere, or both. In fact, their values for the right hemisphere look nearly the same as their values for the left hemisphere, while controls show a marked increase in values for the left hemisphere over the right. Out of these results arises a strong trend for right hemisphere areas to be more highly connected functionally in the TBI group. While preliminary, this trend is consistent with imaging studies showing more (or more widespread) right hemisphere activation in TBI groups in a range of cognitive tasks. Together, these results begin to reveal a picture where there is unusual reliance upon the right hemisphere along with the left in situations where controls typically favor the left alone. The current results further suggest that these right hemisphere contributions occur even during relative rest periods.

Correlationally, evidence was found in all three experiments for benefits due to education and deficits related to age. Not only did this apply to the typical response times and accuracy measures, but there was some reason to believe that age could play a role in functional connectivity as well, even though the correlations found here did not reach significance. Higher best GCS in the first 24 hours correlated both with higher accuracy (Experiment 1) as well as greater functional connectivity values (Experiment 3). These findings suggest that best 24 hour GCS may be a useful measure of severity, at least in areas where head trauma cases are commonly treated with breathing assistance and paralytic medications on the scene. The results further suggest that injury severity, at least by this measure, is related to both behavioral performance and functional connectivity. It remains to be seen, however, what having higher functional connectivity ratings at rest means for performance on cognitive tasks or for recovery.

The reason language processing after TBI is so ambiguous in the literature may be because it is affected only when executive demands are high. What happens when they are is still unclear, but Banich's theory (1998; 2003) goes far in providing an explanation that can encompass multiple open questions associated with TBI. When executive functioning is compromised after TBI due to injury to white matter tracts connecting the distributed executive system or areas directly involved therein, it may result in the person with TBI having a lower threshold for considering an event to be complex. As per Banich, the hemisphere opposite to where processing began is recruited during these kinds of situations, leading to the result that the other hemisphere may be more often recruited by people with TBI. As many language situations (like simple word naming, etc.) do not reach this threshold for most people with TBI, studies using such tasks find no evidence of impairment. During more difficult tasks, the other hemisphere is recruited, which will lead to response slowing and may be at least partially responsible for the speed of processing effects that are so pervasive in the TBI literature and yet have received so little mechanistic explanation. In untimed tasks or tasks with slower pacing, the recruitment of the other hemisphere may not result in a decrement in accuracy of performance, but fast-paced tasks may elicit less accurate responding. Both findings are common in the literature. These ideas are consistent with the findings in the current study, in that there was response slowing and lower accuracy in the TBI group as compared to controls, but also because the TBI group did significantly worse in cases when executive demands were higher. Finally, this theory of other hemisphere recruitment also sheds light on the frequent neuroimaging finding after TBI showing greater involvement of the right hemisphere (e.g., Christodoulou, et al. 2001).

While satisfying, this explanation when applied to cognition after TBI represents purely a hypothesis. What is needed now is for studies to be designed that look specifically at hemispheric recruitment during complex cognitive tasks in people with TBI. There are multiple ways to go about this. First, measurements can be taken of interhemispheric transfer time in people with TBI and control participants, using typical methods like the crossed-uncrossed reaction time paradigm with visual and/or tactile stimulation, or EEG. These measurements can then be used to compare slowdown times for each person and each group during behavioral performance of a cognitive task which increases in complexity parametrically. The complexity scaling should be great enough that both groups should reach a point at which the task becomes nearly too complex to manage. The step below that for each person would be a good point to see whether recruitment of the other hemisphere is taking place. Again, hemispheric presentation of items would be useful, as recruitment of the opposite hemisphere may be task- and/or hemisphere-dependent. While this type of behavioral experiment would be important, this is the kind of question which would really lend itself favorably to neuroimaging, especially time-sensitive methods like ERP, MEG, or fNIRS. The idea here would be to track patterns of activation during cognitive tasks of increasing complexity, to see if evidence could be found that a) people in both groups recruit both hemispheres during more complex parts of the task, and b) people with TBI have a lower threshold for doing this than do controls.

If this is found to be true, what would the implications of such a finding be for healthcare professionals who see people with TBI? The answers are not simple and depend on the immediate goals of the intervention. Hemispheric presentation could be used in a variety of ways. Given the increase in benefits for items presented in the right visual field shown in the current studies, it may be helpful to utilize RVF presentation methods for space-limited materials which the person with TBI may need some help in processing. On the other hand, left visual field or bilateral presentations might encourage recovery of control-like hemispheric recruitment patterns. These are not exclusive ideas, but neither one has accrued enough support to be worth suggesting seriously. More importantly, it remains to be seen what hemispheric use differences mean in terms of outcomes. When the TBI pattern is different from the control pattern it’s not clear yet whether it is adaptive or maladaptive. We tend to assume since people with TBI perform below controls that disordered processes are at work, but they could actually represent better performance than an unseen alternative. It’s also not known how patterns of hemispheric recruitment change during recovery, and what kinds of initial patterns and changes are associated with good vs. poor functional outcomes. Before these questions have been addressed by future research, it is difficult to even speculate how these findings could enhance treatment protocols.

In the meantime, however, the current research has demonstrated that, while patterns of responding to low-level language stimuli may be similar in persons with TBI and controls, there are important differences between them. The first difference comes about when the executive demands in support of language processing are high—in cases like these, people with TBI appear to have more difficulty. Hemispheric recruitment also seems to be different in the two groups tested, such that a stronger right visual field advantage was seen in the TBI group. Finally, the functional connectivity analysis, while admittedly preliminary, was suggestive that for at least some people with TBI, functional connectivity at rest may be stronger than control levels. Together these findings begin to paint a complex picture where hemispheric and executive factors have important bearing upon language processing in people with TBI.

APPENDIX A

SEMANTIC PRIMING AFTER TBI

A.1 INTRODUCTION

Information on priming after traumatic brain injury is scarce, and whether people with TBI are using semantic information to help in language processing is not known. A reasonably comprehensive search of the literature fails to find studies using semantic priming with lexical decision as a task at all. There are a few studies in this population looking at facilitation of previously presented information, however. Vakil, Jaffe, Eluze, Groswasser, & Aberbuch (1996) found that repetition in reading a list of words helped reading times for both persons with traumatic brain injury as well as controls. Vakil & Sigal (1997) used categories that were previously presented or not and recorded how many nonfrequent category members were generated. Their control and TBI groups both generated more nonfrequent category members to primed categories than nonprimed categories. Finally, Vakil & Oded (2003) obtained similar results with a word stem completion paradigm. Together these results suggest that persons with TBI can show benefit from prior presentations of information, including semantic information, in typical memory tasks. What remains to be seen is whether this type of benefit can be used in language processing as well.

This project is part of a larger project looking at various types of language information use after traumatic brain injury (Russell, Scanlon, Arenth, & Ricker, in prep). The selection of the data reported here was meant to establish the fact that semantic priming in a lexical decision task does occur in people with TBI, even when simple reaction time measures do not discriminate between them and a control group. All participants saw semantically related and unrelated word pairs, as well as pairs with one word and one nonword. Based on previous work showing previously presented information can be used implicitly in people with TBI as well as work showing relatively unimpaired low-level language in the same population, it was expected that both groups would show the expected benefit of related trials as compared to unrelated trials reported in multiple studies (as originally described in Meyer & Schvaneveldt, 1971).

A.2 METHOD

A.2.1 Participants

Final recruitment for this experiment was 14 control participants and 12 persons with TBI. In order to best match performance, the 2 extra controls' data has been set aside, and all results described below are on 12 pairs of participants, matched for age, gender, and years of education. Included are 11 pairs of males, and 1 pair of females. This gender distribution reflects the fact that males are more likely to suffer traumatic brain injury—estimates derived from local clinicians suggest at least 75% of people to be seen with TBI in recent history are males. Means for age and years of education did not differ significantly between groups (Age: Controls: M = 39.92, SD = 10.56, TBI: M = 41.17, SD = 10.18; t(22) = -0.30, p = 0.77; Education: Controls: M = 14.00, SD = 1.95, TBI: M

= 13.83, SD = 1.90, t(22) = 0.21, p = 0.83). Seven participants from the TBI group and three from the control group also participated in the experiments described in Chapters 2 and 3.

Causes of injury were predominantly motor vehicle or motorcycle accidents (4 and 6, respectively). One patient's injury was the result of a fall, and one other injury resulted from a falling object. The initial observed Glasgow Coma scores for the TBI group had a range of 3-14, with a mean of 6.25 (SD = 4.67), and a median of 3. Best scores in 24 hours ranged from 6-14, with a mean of 10.33 (SD = 3.03), and a median of 11. All but two participants received an injury classification of severe; the remaining three were designated complicated mild. Time since injury ranged from 0.98 to 2.93 years, with a mean of 1.68 years (SD = 0.71), and a median of 1.39 years.

No participants reported any psychological, neurological, or substance abuse disorder, or any sensory or motor difficulties that would have precluded them from completing the task. All were right-hand dominant, and native speakers of English.

A.2.2 Stimuli, Design, and Procedure

These tasks were run as part of a larger experiment (described in Russell, et al., in prep.) which included multiple computerized language tests based on classic psycholinguistic paradigms as well as related subtests from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983). All participants gave informed consent as approved by the University of Pittsburgh's Institutional Review Board, and were compensated $10/hour for their participation. All tasks were completed in one session.

A.2.2.1 Basic Response Time Measure

In order to ensure that any differences in reaction time measures between groups were due to cognitive, and not motor features, a measure of simple response time was given. Subjects were asked to make a button-press response as fast as they could each time a large blue circle was displayed on a computer screen. Response times were collected.

A.2.2.2 Semantic Priming

As part of a larger task, 20 semantically related and 20 unrelated pairs of words were presented (the full experiment also included equal numbers of orthographically and phonologically related pairs as well as repetition pairs, Russell et al., in prep.). Five of each trial type were converted by changing a vowel so that the second word was a nonword. Semantic and unrelated trials did not differ significantly in frequency as determined by the Kucera and Francis norms (accessed at http://www.psy.uwa.edu.au/mrcdatabase/mrc2.html). Trials consisted of a 2000 millisecond screen with a centered plus sign for orienting attention followed by a 300 ms central presentation of the prime word and then a central presentation of the target word. The latter remained on the screen for 5000 ms or until the participant made a button-press response. E-prime software (www.pstnet.com) and a laptop computer were used for stimulus presentation and response collection. Data collected included response times and accuracy values.

A.3 RESULTS

A.3.1 Basic Response Time Measure

Response times were not significantly different between the groups (t(20) = -0.53, $p = 0.60$). This result suggests that there is no motoric reason that the groups should differ in the rest of the subtests. Any differences found should be able to be ascribed to differences in the speed of cognition.

A.3.2 Semantic Priming

Repeated measures ANOVAs were computed on the response time and accuracy data with group status (control, TBI) and pair type (related, unrelated) as factors. Planned comparisons for pair type were then computed for each group separately. The analysis of response times revealed that related trials were significantly faster than unrelated trials (related trials: M = 824.72, SD = 294.37; unrelated trials: M = 921.65, SD = 315.52; F(1, 22) = 72.78, $p < 0.001$). Please see Figure A.1. for a graphical representation of this effect. There was no significant effect of group (F(1,22) = 0.57, $p = 0.46$) or group x relatedness interaction (F(1,22) = 0.51, $p = 0.48$). Planned comparisons showed that the priming effect was seen in both the control (t(11) = -7.64, $p < 0.001$) and TBI (t(11) = -4.91, $p < 0.001$) groups.

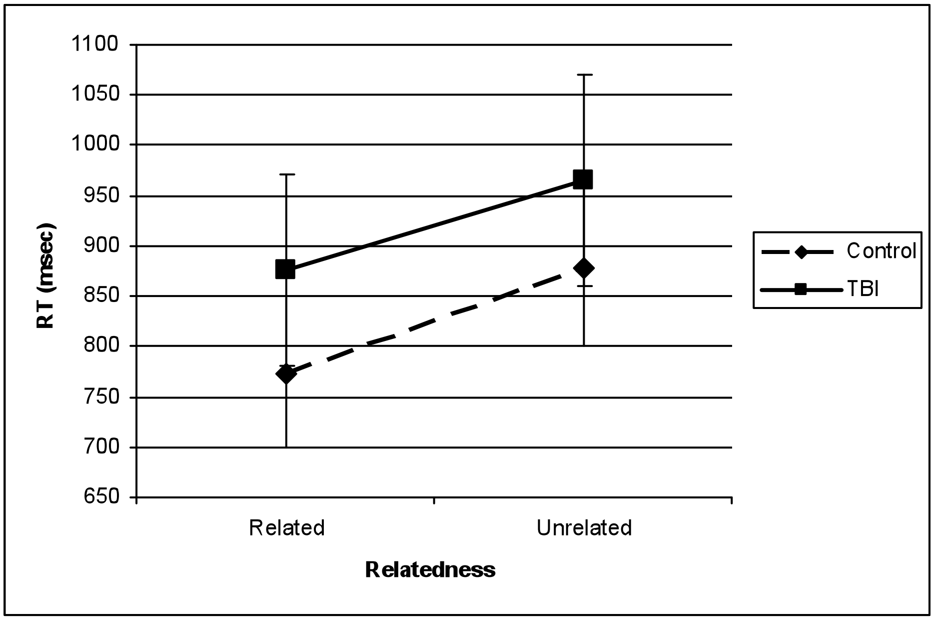

Figure A.5.1 Priming effects in both groups, with no group difference.

A.4 DISCUSSION

The data presented in this appendix show that both groups experienced typical semantic priming in that their responses on trials where the two words in the pair were related were faster than those in which they were unrelated. The two groups additionally did not differ on motor or cognitive response times.

APPENDIX B

STIMULI, EXPERIMENT 1

Block	Prime	Target	Type	VF
1	TABLE	BED	RelExp	L
1	CIRCLE	CROSS	RelExp	L
1	ROOF	DOOR	RelExp	L
1	HAIR	FUR	RelExp	L
1	PANTS	HAT	RelExp	L
1	FOX	HORSE	RelExp	L
1	BRASS	IRON	RelExp	L
1	VELVET	LINEN	RelExp	L
1	OAK	MAPLE	RelExp	L
1	GARLIC	THYME	RelExp	L
1	ARM	NOSE	RelExp	R
1	BEAN	ONION	RelExp	R
1	RUBY	OPAL	RelExp	R
1	LEMON	PEAR	RelExp	R
1	JEEP	PLANE	RelExp	R
1	SHARK	TROUT	RelExp	R
1	MUSIC	ART	RelExp	R
1	PAN	BOWL	RelExp	R
1	INCH	MILE	RelExp	R
1	ROSE	DAISY	RelExp	R
1	DUKE	SUDS	UnrelExp	L
1	BELT	FLAME	UnrelExp	L
1	CAT	HONEY	UnrelExp	L
1	CLOWN	KING	UnrelExp	L
1	COAL	NAIL	UnrelExp	L
1	DRESS	PAINT	UnrelExp	L
1	DUCK	PLOW	UnrelExp	L
1	THIEF	SEA	UnrelExp	L

1	HEAT	CHIEF	UnrelExp	L
1	ICE	TIRE	UnrelExp	L
1	LIGHT	TRACK	UnrelExp	R
1	NICKEL	FOREST	UnrelExp	R
1	PAGE	CAR	UnrelExp	R
1	TEARS	CAVE	UnrelExp	R
1	WEB	MILK	UnrelExp	R
1	WOOL	MOUSE	UnrelExp	R
1	BEER	MOON	UnrelExp	R
1	BIRD	MOVIE	UnrelExp	R
1	HEART	STORE	UnrelExp	R
1	DOG	WOOD	UnrelExp	R
1	IGLOO	STALL	FillU	L
1	NICE	CRAWL	FillU	L
1	CRAZY	ELSE	FillU	L
1	BABY	COURT	FillU	L
1	DERBY	SNACK	FillU	L
1	SWEPT	BALL	FillU	L
1	FLOW	COUGH	FillU	L
1	LACE	GLOOM	FillU	L
1	SCAN	STAND	FillU	L
1	STORY	PRANK	FillU	L
1	FOIL	NUDE	FillU	L
1	GLAD	VOICE	FillU	L
1	MOTOR	STUFF	FillU	L
1	BOARD	BRUISE	FillU	L
1	ROOM	LACK	FillU	L
1	STAGE	AWAY	FillU	L
1	OCEAN	BRACE	FillU	L
1	GLOBE	PRICE	FillU	L
1	CURVE	STYLE	FillU	L
1	KEPT	JACK	FillU	L
1	HORNET	STEP	FillU	R
1	PROD	QUEST	FillU	R
1	FLUNG	FOLK	FillU	R
1	CLEFT	SLAVE	FillU	R
1	NORMAL	DELAY	FillU	R
1	GADGET	BRICK	FillU	R
1	JAZZ	PRESS	FillU	R
1	MISS	PATH	FillU	R
1	PLAY	SOME	FillU	R
1	PRETTY	KEEP	FillU	R
1	MAJOR	GROUP	FillU	R
1	MITTEN	CROWD	FillU	R
1	ROAST	BARN	FillU	R

1	POINT	NIGHT	FillU	R
1	CHURCH	PACT	FillU	R
1	ONCE	SCENE	FillU	R
1	NUMBER	PEPPER	FillU	R
1	FALSE	SMOG	FillU	R
1	REPORT	GLUE	FillU	R
1	BLUE	RATTLE	FillU	R
1	FARM	DREAN	NW	R
1	EARTH	BRUVE	NW	R
1	FACT	FANAL	NW	R
1	DULL	FAP	NW	R
1	BORROW	HYLE	NW	R
1	UGLY	CHARK	NW	R
1	MINOR	WRAE	NW	R
1	BLOOD	MACT	NW	R
1	BEEF	LIRD	NW	R
1	GAME	CREMIT	NW	R
1	FRIEND	GLAK	NW	R
1	TWICE	DACT	NW	R
1	LETTER	RIL	NW	R
1	TOWN	DEECE	NW	R
1	PAPER	KRALE	NW	R
1	SOFT	DESS	NW	R
1	THAT	TOISE	NW	R
1	DEVIL	GLECT	NW	R
1	FOUND	BOSH	NW	R
1	WEAK	FANCH	NW	R
1	HELL	BIRL	NW	L
1	MOST	FANDLE	NW	L
1	CARE	PAIT	NW	L
1	SLEEP	FEAP	NW	L
1	FAR	TOLPH	NW	L
1	LAST	FINT	NW	L
1	ABOVE	ZUTE	NW	L
1	WINTER	YULOW	NW	L
1	LEAF	FUES	NW	L
1	HAND	PANTLE	NW	L
1	EARLY	NASIS	NW	L
1	FAD	PAGGED	NW	L
1	ALWAYS	VUR	NW	L
1	LOWER	ORROW	NW	L
1	MIND	NAZZ	NW	L
1	DRUNK	DRIBEN	NW	L
1	LOSS	DAWP	NW	L
1	DINNER	FLASP	NW	L

1	COMB	NEIBON	NW	L
1	KILL	GLART	NW	L
1	COINS	SPOLE	NW	L
1	WAGE	BEAL	NW	L
1	SKILL	AHY	NW	L
1	SORROW	TELON	NW	L
1	SOFA	ELT	NW	L
1	NEWT	REASE	NW	L
1	BRAIN	VIND	NW	L
1	FAMILY	LIG	NW	L
1	FACES	LISS	NW	L
1	TRAMP	RIT	NW	L
1	READY	KOWT	NW	L
1	VEIN	LORG	NW	L
1	STAG	LISH	NW	L
1	SCREW	CLUD	NW	L
1	TIME	RINGLE	NW	L
1	STRIPE	PANY	NW	L
1	EMPTY	GLISS	NW	L
1	YEAR	STOK	NW	L
1	OVER	GOUR	NW	L
1	HURT	TINK	NW	L
1	WHALE	NEGEL	NW	R
1	SHORT	TEGAL	NW	R
1	FIRE	HOBIN	NW	R
1	BROOM	MUK	NW	R
1	LEAST	KEER	NW	R
1	DOCTOR	LAIRY	NW	R
1	WAKE	LANCH	NW	R
1	TIGER	STOGA	NW	R
1	FIRST	LARROW	NW	R
1	BELOW	STITE	NW	R
1	SMALL	HAME	NW	R
1	SUMMER	SPEEF	NW	R
1	TREE	THEL	NW	R
1	THERE	SHEME	NW	R
1	THUMB	MELLY	NW	R
1	SQUARE	PLICE	NW	R
1	CLEAN	MEZAL	NW	R
1	WHITE	SADIO	NW	R
1	BEING	MINGE	NW	R
1	SILVER	ROUCH	NW	R
2	CARROT	CORN	RelExp	L
2	BIRCH	ELM	RelExp	L
2	COAT	GOWN	RelExp	L

2	APPLE	GRAPE	RelExp	L
2	HEAD	LEG	RelExp	L
2	DRUMS	PIANO	RelExp	L
2	DEER	PONY	RelExp	L
2	CAR	SHIP	RelExp	L
2	COTTON	SILK	RelExp	L
2	BACON	STEAK	RelExp	L
2	DESK	STOOL	RelExp	R
2	ORCHID	TULIP	RelExp	R
2	FLEA	ANT	RelExp	R
2	TRAIN	CANOE	RelExp	R
2	LAMP	CHAIR	RelExp	R
2	BEAR	COW	RelExp	R
2	HOUSE	CABIN	RelExp	R
2	BURLAP	FELT	RelExp	R
2	EAR	FOOT	RelExp	R
2	SHOE	GLOVE	RelExp	R
2	FATHER	JAIL	UnrelExp	L
2	BELLY	LOAD	UnrelExp	L
2	TUBE	MOTHER	UnrelExp	L
2	MASTER	JACKET	UnrelExp	L
2	SPACE	DRAIN	UnrelExp	L
2	PRAY	MINK	UnrelExp	L
2	CANARY	LAKE	UnrelExp	L
2	LAND	NEWS	UnrelExp	L
2	HIVE	DRINK	UnrelExp	L
2	WATER	BEE	UnrelExp	L
2	YARD	SPRAY	UnrelExp	R
2	CATTLE	JUDGE	UnrelExp	R
2	GIRL	CLOCK	UnrelExp	R
2	SPICE	BOY	UnrelExp	R
2	PASTE	CARD	UnrelExp	R
2	FRAME	SKY	UnrelExp	R
2	RAT	SLIDE	UnrelExp	R
2	NEST	WORLD	UnrelExp	R
2	WEEP	BEAST	UnrelExp	R
2	BREAD	CRY	UnrelExp	R
2	ENGINE	MOTOR	FillR	L
2	GIN	WINE	FillR	L
2	TIGER	LION	FillR	L
2	ARMY	NAVY	FillR	L
2	DIRT	MUD	FillR	L
2	MINT	CANDY	FillR	L
2	HOME	TENT	FillR	L
2	SPOON	PAN	FillR	L

2	SILVER	GOLD	FillR	L
2	HALL	WINDOW	FillR	L
2	COFFEE	TEA	FillR	L
2	SNOW	HAIL	FillR	L
2	LOTION	CREAM	FillR	L
2	LIZARD	SNAKE	FillR	L
2	FLY	MOTH	FillR	L
2	MINUTE	DECADE	FillR	L
2	VALLEY	CLIFF	FillR	L
2	STEM	PETAL	FillR	L
2	BANANA	PEACH	FillR	L
2	BUS	TRUCK	FillR	L
2	PRIEST	POPE	FillR	R
2	STRING	ROPE	FillR	R
2	DAGGER	RIFLE	FillR	R
2	ROAD	PATH	FillR	R
2	LAWYER	NURSE	FillR	R
2	TACK	NAIL	FillR	R
2	STEEL	IRON	FillR	R
2	AUNT	SON	FillR	R
2	FIGURE	SHAPE	FillR	R
2	BRANDY	VODKA	FillR	R
2	ROBIN	CROW	FillR	R
2	BRUSH	COMB	FillR	R
2	DRUM	FLUTE	FillR	R
2	PENNY	DIME	FillR	R
2	FLOOR	WALL	FillR	R
2	PAN	POT	FillR	R
2	FROWN	SMILE	FillR	R
2	KNIFE	FORK	FillR	R
2	SUGAR	SALT	FillR	R
2	OVEN	STOVE	FillR	R
2	GLASS	AKO	NW	R
2	AREA	HADA	NW	R
2	HERE	WOTE	NW	R
2	FINGER	FUPPLY	NW	R
2	TINY	FURVE	NW	R
2	BLACK	VINK	NW	R
2	HUMAN	GIDAL	NW	R
2	GOLD	VAWL	NW	R
2	LODGE	PODE	NW	R
2	ANSWER	SARRY	NW	R
2	SOAP	HANE	NW	R
2	PRISON	RADGE	NW	R
2	WORST	VAY	NW	R

2	PINK	WONE	NW	R
2	BOUNCE	KIE	NW	R
2	MASS	YOWN	NW	R
2	WHEEL	ALD	NW	R
2	VOTE	PARM	NW	R
2	BOOK	CROOP	NW	R
2	TEETH	DOUND	NW	R
2	STOVE	YAIT	NW	L
2	USHER	GURST	NW	L
2	CHEEK	RAMILY	NW	L
2	RENT	ROMAL	NW	L
2	WEDGE	VAWX	NW	L
2	PRIZE	STOKE	NW	L
2	LOCK	PIRT	NW	L
2	SQUAD	BLEEF	NW	L
2	SCREEN	CLOOR	NW	L
2	CAUSE	ANLE	NW	L
2	FUSS	PHEME	NW	L
2	MONEY	HEEST	NW	L
2	SEAT	YEAKS	NW	L
2	GUIDE	BELOR	NW	L
2	DILL	HOID	NW	L
2	ZEBRA	GAREL	NW	L
2	OLIVE	PLEAN	NW	L
2	RIGID	PAKE	NW	L
2	GNAT	TRAIM	NW	L
2	BAIL	OTEM	NW	L
2	FULL	MIVID	NW	L
2	SWEET	RASTY	NW	L
2	UNDER	MOTIN	NW	L
2	FEAR	RASK	NW	L
2	TRACKS	MULCE	NW	L
2	LONG	PORRY	NW	L
2	BURN	MUNCE	NW	L
2	SWEEP	PLOCK	NW	L
2	OPEN	MURY	NW	L
2	FORK	PATA	NW	L
2	FAST	NAPUR	NW	L
2	JOLT	HIELD	NW	L
2	EYES	NACE	NW	L
2	JOIN	HIRTH	NW	L
2	RHYME	NAKER	NW	L
2	MARCH	SERM	NW	L
2	RACE	BERO	NW	L
2	DANCE	OCRIPT	NW	L

2	TRY	POLT	NW	L
2	WALTZ	JORE	NW	L
2	FUSE	PITE	NW	R
2	BEET	EXA	NW	R
2	NEPHEW	LAMPLE	NW	R
2	STAIN	OCE	NW	R
2	HERBS	NUNG	NW	R
2	LABOUR	GOAP	NW	R
2	VALUE	BEDIT	NW	R
2	THEORY	JODER	NW	R
2	NIECE	DEACH	NW	R
2	RICE	DEGAL	NW	R
2	CROOK	FREL	NW	R
2	CLOAK	MALS	NW	R
2	ROBBER	CET	NW	R
2	STEER	SOPE	NW	R
2	CALL	LETCH	NW	R
2	OBEY	KLOBE	NW	R
2	GIVE	NIREY	NW	R
2	POLKA	SWEAX	NW	R
2	IDEA	HOTE	NW	R
2	PITCH	DAKE	NW	R

Key: RelExp = related, experimental trial; UnrelExp = unrelated, experimental trial; FillR = related, filler trial; FillU = unrelated, filler trial; NW = nonword trial; R = right visual field; L = left visual field

APPENDIX C

STIMULI, EXPERIMENT 2

Items with a Dominant Response

- BATON
- BED
- BEER
- BELL
- BENCH
- BIKE
- BIRD
- BOOK
- BROOM
- CANE
- CHAIR
- CIGAR
- CUP
- DOLL
- DOLLAR
- FINGER
- FIRE
- FOOD
- FORK
- GIFT
- GUM
- GUN
- HAT
- JET
- JOB
- KITE
- KNIFE
- LADDER
- LAKE
- MILK
- NEEDLE
- PEN
- PIANO
- PIPE
- PLANE
- POOL
- RADIO
- RIFLE
- RULER
- SCALE
- SEED
- SHIRT
- SOAP
- SONG
- TOY
- WING

Items with Multiple Likely Responses

BALL
BASKET
BEACH
BOAT
BOX
BRICK
CAT
CLOCK
CRAYON
DOG
FIST
FLAG
FOOT
GLASS
GLOVE
GRAVE
HAMMER
HOSE
ICE
KEY
LAWN
LENS
LETTER
MATCH
MONEY
MOUTH
MOVIE
NOSE
OVEN
PAN
PHONE
PILL
PURSE
RAZOR
ROPE
SCHOOL
SHOE
SINK
STICK
STOVE
SUN
TABLE
TOWEL
WHEEL
WOOD
YARN

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